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Therapeutic hypothermia to reduce intracranial pressure after traumatic brain injury: the Eurotherm3235 RCT

Peter JD Andrews, H Louise Sinclair, Aryelly Rodríguez, Bridget Harris, Jonathan Rhodes, Hannah Watson and Gordon Murray on behalf of the Eurotherm3235 trial collaborators

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Abstract

Therapeutic hypothermia to reduce intracranial pressure after traumatic brain injury: the Eurotherm3235 RCT

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Background: Traumatic brain injury (TBI) is a major cause of disability and death in young adults worldwide. It results in around 1 million hospital admissions annually in the European Union (EU), causes a majority of the 50,000 deaths from road traffic accidents and leaves a further $\approx 10,000$ people severely disabled.

Objective: The Eurotherm3235 Trial was a pragmatic trial examining the effectiveness of hypothermia (32–35 °C) to reduce raised intracranial pressure (ICP) following severe TBI and reduce morbidity and mortality 6 months after TBI.

Design: An international, multicentre, randomised controlled trial.

Setting: Specialist neurological critical care units.

Participants: We included adult participants following TBI. Eligible patients had ICP monitoring in place with an ICP of > 20 mmHg despite first-line treatments. Participants were randomised to receive standard care with the addition of hypothermia (32–35 °C) or standard care alone. Online randomisation and the use of an electronic case report form (CRF) ensured concealment of random treatment allocation. It was not possible to blind local investigators to allocation as it was obvious which participants were receiving hypothermia. We collected information on how well the participant had recovered 6 months after injury. This information was provided either by the participant themselves (if they were able) and/or a person close to them by completing the Glasgow Outcome Scale – Extended (GOSE) questionnaire. Telephone follow-up was carried out by a blinded independent clinician.

Interventions: The primary intervention to reduce ICP in the hypothermia group after randomisation was induction of hypothermia. Core temperature was initially reduced to 35 °C and decreased incrementally to a lower limit of 32 °C if necessary to maintain ICP at < 20 mmHg. Rewarming began after 48 hours if ICP remained controlled. Participants in the standard-care group received usual care at that centre, but without hypothermia.

Main outcome measures: The primary outcome measure was the GOSE [range 1 (dead) to 8 (upper good recovery)] at 6 months after the injury as assessed by an independent collaborator, blind to the intervention. A priori subgroup analysis tested the relationship between minimisation factors including being aged < 45 years, having a post-resuscitation Glasgow Coma Scale (GCS) motor score of < 2 on admission, having a time from injury of < 12 hours and patient outcome.

Results: We enrolled 387 patients from 47 centres in 18 countries. The trial was closed to recruitment following concerns raised by the Data and Safety Monitoring Committee in October 2014. On an intention-to-treat basis, 195 participants were randomised to hypothermia treatment and 192 to standard care. Regarding participant outcome, there was a higher mortality rate and poorer functional recovery at 6 months in the hypothermia group. The adjusted common odds ratio (OR) for the primary statistical analysis of the GOSE was 1.54 [95% confidence interval (CI) 1.03 to 2.31]; when the GOSE was dichotomised the OR was 1.74 (95% CI 1.09 to 2.77). Both results favoured standard care alone. In this pragmatic study, we did not collect data on adverse events. Data on serious adverse events (SAEs) were collected but were subject to reporting bias, with most SAEs being reported in the hypothermia group.

Conclusions: In participants following TBI and with an ICP of > 20 mmHg, titrated therapeutic hypothermia successfully reduced ICP but led to a higher mortality rate and worse functional outcome.

Limitations: Inability to blind treatment allocation as it was obvious which participants were randomised to the hypothermia group; there was biased recording of SAEs in the hypothermia group. We now believe that more adequately powered clinical trials of common therapies used to reduce ICP, such as hypertonic therapy, barbiturates and hyperventilation, are required to assess their potential benefits and risks to patients.

Trial registration: Current Controlled Trials ISRCTN34555414.

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Contents

| | |
|---|--------------|
| List of tables | xi |
| List of figures | xiii |
| List of boxes | xv |
| List of supplementary material | xvii |
| List of abbreviations | xix |
| Plain English summary | xxi |
| Scientific summary | xxiii |
| Chapter 1 Literature review: from bench to bedside | 1 |
| Background and objectives | 1 |
| Pathophysiology | 1 |
| <i>Blood–brain barrier</i> | 2 |
| <i>Inflammation and oedema</i> | 2 |
| <i>Metabolism</i> | 2 |
| <i>Excitotoxicity</i> | 3 |
| Cerebrovascular effects | 3 |
| <i>Intracellular calcium-dependent signalling</i> | 3 |
| <i>Neuronal cell death</i> | 4 |
| The Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies | 4 |
| Review of clinical evidence | 4 |
| <i>Induction of hypothermia</i> | 5 |
| <i>Meta-analyses</i> | 6 |
| Rationale for the Eurotherm3235 Trial | 7 |
| Chapter 2 Trial design | 9 |
| Specific trial objectives and hypotheses | 9 |
| <i>Hypothesis</i> | 9 |
| <i>Research questions</i> | 9 |
| Methods | 9 |
| <i>Trial design</i> | 9 |
| <i>Important changes to methods after trial commencement</i> | 11 |
| Participants | 11 |
| <i>Inclusion criteria</i> | 12 |
| <i>Exclusion criteria</i> | 12 |
| <i>Premature withdrawal</i> | 13 |
| Settings and locations where the data were collected | 13 |
| <i>Trial site initiation visits</i> | 13 |
| <i>Site initiation visits for the non-UK sites</i> | 14 |
| Interventions | 14 |

| | |
|---|-----------|
| Outcomes | 15 |
| <i>Primary</i> | 15 |
| <i>Secondary</i> | 15 |
| <i>Primary end-point data collection</i> | 15 |
| <i>Follow-up procedure for UK centres</i> | 16 |
| <i>Follow-up procedure for non-UK centres</i> | 17 |
| Secondary end-point data collection | 17 |
| <i>Any changes to trial outcomes after the trial commenced, with reasons</i> | 17 |
| Sample size | 17 |
| <i>Data monitoring</i> | 18 |
| <i>Statistical guidelines for termination: Data and Safety Monitoring Committee charter</i> | 18 |
| Randomisation | 19 |
| <i>Type of randomisation</i> | 19 |
| <i>Implementation</i> | 19 |
| <i>Blinding</i> | 19 |
| Statistical methods | 20 |
| <i>Overall statistical principles</i> | 20 |
| <i>Statistical analysis plan</i> | 20 |
| <i>Population for analysis</i> | 21 |
| <i>List of analyses</i> | 21 |
| <i>Primary outcome</i> | 22 |
| <i>Secondary outcomes</i> | 23 |
| Quality control of summary tables and statistical analysis | 24 |
| <i>Quality control/validation: summary tables</i> | 24 |
| <i>Quality control/validation: statistical analysis</i> | 24 |
| Unblinding procedures | 24 |
| Chapter 3 Results | 25 |
| Results | 25 |
| <i>Participant flow</i> | 25 |
| <i>Recruitment</i> | 25 |
| <i>Why the trial was ended</i> | 25 |
| <i>Baseline data</i> | 25 |
| <i>Numbers analysed</i> | 25 |
| <i>Outcomes and estimation</i> | 25 |
| <i>Ancillary analyses</i> | 40 |
| <i>Harms</i> | 41 |
| Economic evaluation | 42 |
| Chapter 4 Discussion | 43 |
| Discussion | 43 |
| Limitations | 44 |
| <i>Generalisability</i> | 44 |
| Chapter 5 Updated systematic review of therapeutic hypothermia for adult patients following traumatic brain injury | 47 |
| Evidence before this study | 47 |
| Added value of this study | 47 |
| Implications of all the available evidence | 47 |
| Introduction | 47 |
| Aims | 48 |

| | |
|---|---------------|
| Materials and methods | 48 |
| <i>Search methods for identification of trials</i> | 48 |
| <i>Ethics approval and consent</i> | 48 |
| <i>Methodological criteria for selection of randomised controlled trials</i> | 48 |
| <i>Data extraction</i> | 48 |
| <i>Statistical analyses</i> | 49 |
| <i>Sensitivity analysis</i> | 49 |
| Results | 49 |
| <i>Risk of bias of included randomised controlled trials</i> | 50 |
| <i>Quality of included randomised controlled trials</i> | 50 |
| Primary aims | 51 |
| <i>Mortality results</i> | 51 |
| <i>Mortality results with quality and risk-of-bias analysis</i> | 51 |
| <i>Poor outcomes</i> | 51 |
| <i>Poor outcome results with quality and risk-of-bias analysis</i> | 51 |
| <i>New pneumonia results</i> | 51 |
| <i>New pneumonia results with quality and risk-of-bias analysis</i> | 51 |
| Secondary aims | 57 |
| <i>Mortality: comparison of control groups and comparison of controlled normothermia temperature ranges</i> | 57 |
| <i>Early therapeutic hypothermia compared with late therapeutic hypothermia</i> | 57 |
| <i>Mortality: effect of duration of follow-up</i> | 57 |
| <i>Mortality: date of publication</i> | 57 |
| Discussion | 61 |
| <i>Summary of results</i> | 61 |
| <i>Explanation of results</i> | 61 |
| <i>Quality of evidence</i> | 61 |
| <i>Deviation from systematic review protocol</i> | 62 |
| <i>Limitations of the review</i> | 62 |
| <i>Similarities to, and differences from, other reviews</i> | 62 |
| <i>Ongoing trials of therapeutic hypothermia for traumatic brain injury</i> | 62 |
| Conclusions | 63 |
| <i>Key messages</i> | 63 |
| Chapter 6 A biological effect or an imbalance of co-interventions? Exploratory analyses of the Eurotherm3235 Trial | 65 |
| Introduction | 65 |
| Background | 65 |
| Material and methods | 65 |
| <i>Statistical analysis</i> | 66 |
| Results | 66 |
| <i>Data</i> | 66 |
| <i>Demographics and baseline characteristics</i> | 66 |
| <i>Additional data collection sample mortality</i> | 69 |
| Clinical management and interventions | 70 |
| <i>Intracranial pressure management: medical therapy</i> | 70 |
| <i>Intracranial pressure management: surgical treatment</i> | 70 |
| <i>Follow-up computed tomography</i> | 71 |
| <i>Sedation and analgesia</i> | 73 |
| <i>Cardiovascular support</i> | 74 |
| <i>Steroids</i> | 75 |
| <i>Fluid balance</i> | 75 |
| <i>Laboratory results and organ failure</i> | 75 |

| | |
|---|------------|
| <i>Acid–base estimation</i> | 76 |
| <i>Organ dysfunction</i> | 77 |
| <i>Immunity and infection</i> | 78 |
| <i>Coenrolment</i> | 78 |
| <i>Method of cooling</i> | 78 |
| Discussion | 80 |
| Chapter 7 Conclusions | 83 |
| Impact of patient and public involvement, challenges of patient and public involvement and lessons learnt | 83 |
| Conclusions | 84 |
| Acknowledgements | 85 |
| References | 89 |
| Appendix 1 Induction and maintenance of therapeutic hypothermia | 101 |
| Appendix 2 Detection and treatment of shivering | 103 |
| Appendix 3 Data Safety Monitoring Committee charter | 105 |
| Appendix 4 Systematic review protocol: PROSPERO international prospective register of systematic reviews | 115 |
| Appendix 5 Characteristics of included randomised controlled trials | 125 |
| Appendix 6 Comparison of included trials from previous systematic reviews and meta-analyses | 129 |
| Appendix 7 Quality assessment with academic bias | 131 |
| Appendix 8 Modified Jadad scores for included randomised controlled trials | 133 |

List of tables

| | |
|--|-----------|
| TABLE 1 Baseline demographic and clinical characteristics for each group | 27 |
| TABLE 2 Recruitment and treatment allocation by centre | 29 |
| TABLE 3 Participant recruitment by centre and country | 31 |
| TABLE 4 Detailed breakdown of the score category per group for both the full eight-point GOSE, the collapsed six-category GOSE and the dichotomised GOSE | 33 |
| TABLE 5 Results of the primary analysis (hypothermia vs. standard care) and primary subgroup analyses using the ITT population | 34 |
| TABLE 6 Results of the secondary end-point analyses | 35 |
| TABLE 7 Baseline demographic and clinical characteristics for each PP group | 36 |
| TABLE 8 The outcome per group for the full eight-point GOSE, the collapsed six-category GOSE and the dichotomised GOSE in the PP population | 38 |
| TABLE 9 The results of the primary analysis (hypothermia vs. standard care) and primary subgroup analyses in the PP population | 39 |
| TABLE 10 Results of the secondary end-point analyses for the PP population | 39 |
| TABLE 11 Incidence of treatment escalation or stage 2 therapy failure across groups | 40 |
| TABLE 12 Details of all SAEs that were collected throughout the trial | 41 |
| TABLE 13 Summary of baseline demographic, mechanism of injury, time from injury, clinical and radiological presentation, comorbidities and pre-ICU secondary insults data | 67 |
| TABLE 14 Primary outcome of the additional data collection population: likely causes of death | 70 |
| TABLE 15 Medical and surgical management for raised ICP after randomisation | 71 |
| TABLE 16 Marshall classification on follow-up CT and type of craniectomy | 72 |
| TABLE 17 Sedation and analgesia used after randomisation | 74 |
| TABLE 18 Cardiovascular support after randomisation | 74 |
| TABLE 19 Corticosteroids prescribed during ICU admission and fluid balance after randomisation | 75 |
| TABLE 20 Laboratory results at randomisation | 76 |

| | |
|--|-----------|
| TABLE 21 Complications and organ dysfunction after randomisation and organ dysfunction quantified using a modified abbreviated SOFA score | 77 |
| TABLE 22 Infection and antibiotic usage after randomisation | 79 |

List of figures

| | |
|---|------------|
| FIGURE 1 Study flow chart | 10 |
| FIGURE 2 Three stages of ICP management after TBI | 11 |
| FIGURE 3 The CONSORT flow diagram | 26 |
| FIGURE 4 Recruitment graph | 27 |
| FIGURE 5 Kaplan–Meier survival curves per group | 33 |
| FIGURE 6 Intracranial pressure control per group | 35 |
| FIGURE 7 Temperature control per group | 36 |
| FIGURE 8 The PRISMA flow diagram | 50 |
| FIGURE 9 Forest plot of mortality data for 20 studies | 52 |
| FIGURE 10 Mortality results with quality and modified Jadad score assessment of risk-of-bias analysis | 53 |
| FIGURE 11 Forest plot of mortality results with quality and Cochrane Collaboration assessment of risk-of-bias analysis | 54 |
| FIGURE 12 Forest plot of poor outcome | 55 |
| FIGURE 13 Forest plot of new pneumonia data | 56 |
| FIGURE 14 Forest plot of mortality analysed accounting for timing of TH from time of TBI | 58 |
| FIGURE 15 Forest plot of the effect of duration of follow-up on trial results | 59 |
| FIGURE 16 Forest plot of the effect of date of publication on outcome | 60 |
| FIGURE 17 Survival curve between randomisation and 6 months by treatment allocation in the additional data collection cohort | 70 |
| FIGURE 18 Shivering treatment guideline | 104 |

List of boxes

| | | |
|--------------|--|------------|
| BOX 1 | Induction and maintenance of hypothermia guideline | 101 |
| BOX 2 | Rewarming guideline | 102 |
| BOX 3 | Shivering detection guideline | 103 |
| BOX 4 | Shivering detection guideline: shivering assessment tool | 103 |

List of supplementary material

Report Supplementary Material 1 PROSPERO registration

Report Supplementary Material 2 Cochrane domain-based assessment of bias

Supplementary material can be found on the NIHR Journals Library report project page (www.journalslibrary.nihr.ac.uk/programmes/hta/110130/#/documentation).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

| | | | |
|---------|--|-------------------|--|
| AE | adverse event | ICU | intensive care unit |
| ARDS | acute respiratory distress syndrome | IMPACT | International Mission on Prognosis and Clinical Trial Design in Traumatic Brain Injury |
| ATP | adenosine triphosphate | | |
| BBB | blood–brain barrier | IQR | interquartile range |
| B-HYPO | Brain Hypothermia study | ITT | intention to treat |
| CENTRAL | Cochrane Central Register of Controlled Trials | MAP | mean arterial pressure |
| CI | confidence interval | MOF | multiorgan failure |
| CNS | central nervous system | MOHS | Modified Oxford Handicap Scale |
| CONSORT | Consolidated Standards of Reporting Trials | MRC | Medical Research Council |
| CPP | cerebral perfusion pressure | OHDC | oxyhaemoglobin dissociation curve |
| CRASH | Corticosteroid Randomisation After Significant Head Injury | OR | odds ratio |
| CRF | case report form | PbtO ₂ | brain tissue oxygen tension |
| CT | computed tomography | PKC | protein kinase C |
| DMEC | Data Monitoring and Ethics Committee | POLAR | Prophylactic Hypothermia trial to Lessen Traumatic Brain Injury |
| DSMC | Data and Safety Monitoring Committee | PP | per protocol |
| EU | European Union | PRIS | propofol-related infusion system |
| GCS | Glasgow Coma Scale | RCT | randomised controlled trial |
| GOS | Glasgow Outcome Scale | RR | risk ratio |
| GOSE | Glasgow Outcome Scale – Extended | RRT | renal replacement therapy |
| HR | hazard ratio | SAE | serious adverse event |
| ICP | intracranial pressure | SOFA | sequential organ failure assessment |
| | | TBI | traumatic brain injury |
| | | TH | therapeutic hypothermia |

Plain English summary

Following a blow to the head [traumatic brain injury (TBI)], the brain can swell like a bruise, but is enclosed within the skull. If the brain swells, it can lead to a build-up of pressure that can cause damage to parts of the brain. Many patients who have suffered a traumatic brain injury are admitted to an intensive care unit. This is usually because they have become unconscious as a result of the brain injury. These patients require specialised care and often cannot breathe well enough for themselves. They are therefore sedated and attached to a breathing machine, called a ventilator.

This study included 387 participants and looked at whether or not cooling the body down to between 32 and 35 °C within 10 days of injury to try to reduce any brain swelling affected longer-term recovery from TBI. Each participant was randomly allocated to receive either the usual care given or the usual care with the additional treatment of cooling the body to between 32 and 35 °C for at least 48 hours.

The study was stopped early because of concerns about safety raised by the independent Data and Safety Monitoring Committee and agreed by the Trial Steering Committee. The results of this study showed that more patients died after receiving hypothermia than standard care alone and that the survivors who had received hypothermia made a less good recovery than those receiving standard care alone.

It was concluded that hypothermia should not be used to reduce pressure after a TBI.

Scientific summary

Background

Traumatic brain injury (TBI) is damage to the brain caused by trauma from incidents such as falls, traffic accidents and assault. It is a major cause of death and severe disability throughout the world and leads to around 1 million hospital admissions each year throughout the European Union (EU). TBI causes the majority of the 50,000 deaths from road traffic accidents and leaves 10,000 patients severely disabled each year; three-quarters of these victims are young people. This has a devastating emotional and physical impact and presents an enormous financial burden.

One of the most harmful consequences of TBI is cell injury and cell death in the brain. When this occurs, it starts a complex sequence of harmful, and potentially irreversible, processes at the cellular level. These processes can cause swelling (oedema) in the brain. This swelling increases the pressure inside the head and makes the injury worse. Preventing cell injury and death is therefore an important part of treatment. Cell death can occur from minutes to hours after injury and the harmful effects can last for 72 hours or longer. Thus, there may be a window of opportunity of several hours, or even days, during which cell death can be prevented by treatments such as hypothermia. Hypothermia treatment lowers the patient's temperature to below normal, which has a potentially beneficial effect on a number of problems caused by injury to brain cells.

In total, 29 studies in patients have been performed to assess the effects of hypothermia after TBI. These were of varying size and quality, but all observed reduced brain swelling and pressure levels inside the skull during hypothermia treatment. Thirteen of these studies reported significant improvements in patient outcome, with fewer deaths and less disability associated with hypothermia treatment.

Six major reviews of hypothermia studies were published between 2000 and 2008. Each review included differing numbers of trials, with varying quality of randomisation and blinding procedures. All six reviews found a trend towards positive effects of hypothermia on patient outcome, although only two reviews could statistically prove this. The most recent review included eight trials that enrolled comparable patient groups at entry to the trial (baseline). Hypothermia was found to reduce mortality by 20%, although this was not statistically proven. Further analysis showed that this effect was greatest when hypothermia was maintained for > 48 hours. Hypothermia was also associated with a trend towards improvement in patient outcome when measured by the Glasgow Outcome Scale (GOS) at 6 months.

A criticism of these reviews is that most failed to take account of important differences in patient groups (such as those with or without a build-up of pressure due to brain swelling) and differences in treatment protocols, except the use of hypothermia. Only two assessed whether or not the length of hypothermia treatment and speed of rewarming the body afterwards made a difference to the effectiveness of hypothermia. Results suggested that hypothermia treatment lasting for > 48 hours and rewarming rates of 24 hours, or 1 °C over 4 hours, may be factors that are important in reducing deaths and improving disability. However, the studies included in the review did not enrol enough patients to prove this.

In summary, the evidence from previous research shows that hypothermia treatment may be an effective therapy to improve outcome in patients who have suffered a TBI. Many trials have been carried out in this patient group, but none has been extensive enough to prove whether or not hypothermia is effective in preventing further brain damage and reducing death and disability. The Eurotherm3235 Trial aimed to provide a clear answer to this question.

Objectives

- Does therapeutic hypothermia (TH) (32–35 °C) improve patient outcome and reduce mortality 6 months after TBI as assessed by the Glasgow Outcome Scale – Extended (GOSE) questionnaire?

Secondary research questions:

- Does TH (32–35 °C) reduce intracranial hypertension?
- Is TH a cost-effective treatment to improve patient outcome after TBI?

Design

The Eurotherm3235 Trial was a pragmatic, multicentre randomised controlled trial (RCT) to examine the effects of hypothermia (32–35 °C) on patient outcome after TBI. The study recruited for 41 months.

Randomisation

Participants were randomised as soon as possible after meeting the inclusion criteria. The randomisation of participants to receive standard care with the addition of induced TH or standard care alone was undertaken using a central internet-based randomisation service.

Treatment allocation was minimised using the following baseline covariates:

- trial centre
- aged < 45 years or ≥ 45 years
- post-resuscitation Glasgow Coma Scale (GCS) motor component score of 1 or 2 or 3–6
- time from injury < 12 hours or ≥ 12 hours
- pupils – both reacting or one or neither reacting.

Participants allocated to the standard-care group received usual care without TH. Participants randomised to the intervention group received usual care with the addition of TH. Hypothermia was initiated with 20–30 ml/kg of refrigerated 0.9% saline given intravenously and maintained using the cooling technique available at each centre.

The depth of hypothermia (32–35 °C) was guided by intracranial pressure (ICP), with a higher pressure level warranting a cooler target temperature. TH of 32–35 °C was maintained for at least 48 hours and continued for as long as was necessary to reduce and maintain ICP at < 20 mmHg.

Blinded outcome assessment

The primary end point was patient outcome 6 months after TBI, assessed using the GOSE questionnaire. It was not possible to blind local investigators to allocation as it was clinically obvious which participants were receiving hypothermia because of, for example, the equipment required, participant temperature, blood results and fluid requirements. A blinded researcher therefore carried out participant outcome data assessment.

Setting

Induced hypothermia is a specialist intervention; therefore, only neurological ICUs that were familiar with the use of hypothermia treatment in this patient group were included. A total of 61 specialist neurological ICUs were opened as recruiting centres across 18 countries between 2009 and 2015: Belgium ($n = 8$), England ($n = 21$), Estonia ($n = 1$), Germany ($n = 1$), Greece ($n = 6$), Hungary ($n = 1$), India ($n = 3$), Ireland ($n = 1$), Italy ($n = 5$), Northern Ireland ($n = 1$), the Netherlands ($n = 1$), Portugal ($n = 1$), Russia ($n = 1$), Saudi Arabia ($n = 1$), Scotland ($n = 3$), Spain ($n = 4$), Abu Dhabi ($n = 1$) and Wales ($n = 1$).

Participants

Patients were assessed for eligibility to enter the trial on admission to the ICU by the health-care team. They continued to be screened for up to 10 days after the brain injury. If consent was given by the nearest relative/welfare guardian on the patient's behalf, the patient could enter the study and be randomised if/as soon as he or she met the inclusion criteria.

Interventions

Participants who were allocated to the hypothermia treatment group continued to receive their usual care along with having their temperature lowered to between 32 and 35 °C. The depth of cooling was guided by the severity of brain swelling, with more severe brain swelling warranting a lower temperature.

The participant's temperature was lowered in two stages.

Stage 1: induction of hypothermia

Participants were given 20–30 ml/kg of refrigerated 0.9% saline by a drip over 20–30 minutes. This quickly reduced their temperature to around 35 °C.

Stage 2: maintenance of hypothermia

After induction of hypothermia, the participant's temperature had to remain between 32 and 35 °C for at least 48 hours. Temperature could be maintained by using a variety of methods including placing ice packs under the arms and legs or using a special cooling machine. Each study centre used the available method of cooling as this was the most practical way to run the trial in many centres.

Participants were closely monitored for any signs of shivering throughout this period and any observed shivering was treated quickly. We provided a detection and management of shivering guideline to each recruiting centre.

Rewarming phase

No maximum duration of cooling was specified, although the doctor in charge of patient care was asked to consider rewarming the patient after 48 hours of hypothermia treatment. Rewarming was considered if the patient's ICP was stable and < 20 mmHg. Previous studies found that cooling for 48 hours and rewarming within 24 hours reduced deaths and disability in survivors.

Participants allocated to the hypothermia group were rewarmed at a rate of 0.25 °C per hour (1 °C per 4 hours); hence, all participants were rewarmed to normal temperature levels (> 36 °C) within 24 hours.

Treatment escalation

Occasionally, patients who have suffered a brain injury have severe brain swelling that does not respond to the usual treatment methods. These patients often require further treatment with other drugs or, sometimes, surgery. A proportion of participants in the Eurotherm3235 Trial did develop severe brain swelling and required further treatment.

Main outcome measures

The primary outcome was:

- patient outcome at 6 months after TBI, assessed using the GOSE questionnaire.

The secondary outcomes were:

- 6-month mortality rate
- intracranial pressure control
- incidence of pneumonia across both groups
- length of stay in the ICU and hospital
- Modified Oxford Handicap Scale (MOHS) score at 1 month, discharge from the randomising hospital or death, whichever took place first
- correlation between the predicted patient outcome using the MOHS score at hospital discharge and the predicted patient outcome using the GOSE score at 6 months post injury.

Results

We enrolled 387 patients at 47 centres in 18 countries (195 assigned to TH and 192 assigned to standard care) from November 2009 (pilot phase January 2009 to August 2011) to September 2014, when recruitment was suspended following concerns raised by the Data and Safety Monitoring Committee. The mean age of participants was 37 years (range 16–78 years). In total, 15% of TH patients and 18% of patients who received standard care alone were randomised within 12 hours of injury.

The adjusted common odds ratio (OR) for the primary statistical analysis of the GOSE score was 1.53 [95% confidence interval (CI) 1.02 to 2.30]. When the GOSE score was dichotomised, the adjusted common OR was 1.81 (95% CI 1.12 to 2.92). Both ORs were in favour of standard care alone.

Conclusion

In patients with ICP of > 20 mmHg after TBI, titrated hypothermia to reduce ICP led to worse functional outcomes. Future work should study targeted temperature management of < 38 °C and > 36 °C after acute brain injury.

Knowledge landscape after the Eurotherm3235 Trial

We searched RCTs to update the evidence base on the use of TH when administered to adult patients in intensive care following TBI. The main outcomes of interest were mortality, poor (unfavourable) outcomes and new pneumonia.

Secondary aims were (1) comparison of control groups; (2) early (< 24 hours from injury) compared with late (> 24 hours from injury) TH; (3) the effect of duration of follow-up on mortality outcomes; and (4) whether or not the date of publication had any effect on the outcomes of TH trials.

Search methods for identification of trials

Searches were not restricted by date or publication status. Foreign articles published in English were included. The following databases were searched from 1 January 2011 to 31 March 2016: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PubMed and EMBASE. The dates were chosen to be complementary to, and have an overlap of 12 months with, the previous systematic review conducted by one of the co-authors; this was to capture any trials that were in the process of publication.

Other sources

Reference lists of all included trials and relevant review articles were hand-searched by the authors. When appropriate, authors were contacted directly for further information.

Methodological criteria for selection of randomised controlled trials

The inclusion criteria were that trials must (1) be RCTs, (2) investigate adult moderate (i.e. a GCS score of 9–12) or severe (i.e. a GCS score of ≤ 8) TBI and (3) investigate TBI that was sustained following an acute, closed head injury. The use of TH was the intervention of interest. RCTs that did not have two treatment arms with TH compared with a control group were excluded. For the purpose of this review, TH was defined as any intervention with the intention of reducing core body temperature to below the physiological norm (36 °C). The method of temperature reduction was noted during data extraction. Patient outcomes at follow-up were assessed using mortality and poor outcome data. There was a particular emphasis on outcomes recorded on a scale, for example, the GOS, Ranchos Los Amigos Scale or an equivalent scale. Poor outcome reporting includes mortality figures, as per the usual reporting methodology.

Results

The searches identified 21 trials, including data for two new trials. One trial included in the 2014 review has now been published with additional data. These trials enrolled 2299 patients. Only one trial did not include mortality data.

Mortality was reported in 20 studies. When the results of these 20 RCTs were statistically aggregated, there was a significant reduction in mortality in the TH group [risk ratio (RR) 0.84, 95% CI 0.74 to 0.96; $p = 0.01$].

Twenty-one trials reported on poor outcome involving 2286 patients. There were significantly more poor outcomes in the control group than in the TH group (RR 0.81, 95% CI 0.75 to 0.87; $p < 0.00001$). Analysis of the two studies deemed to be at low risk of bias showed that poor outcomes were more likely in the TH group (RR 1.16, 95% CI 1.02 to 1.32; $p = 0.03$). Conversely, analysis of the 19 studies with a high risk of bias combined showed significantly more poor outcomes in the control group than in the TH group (RR 0.70, 95% CI 0.64 to 0.77; $p < 0.00001$).

A subanalysis on mortality specifically assessed the methodology used for temperature management in the control groups. There was no significant difference in mortality between the TH group and the control group with controlled normothermia (RR 0.89, 95% CI 0.74 to 1.08; $p = 0.25$). However, there was significantly greater mortality in the no temperature control group than in the TH group (RR 0.81, 95% CI 0.68 to 0.97; $p = 0.02$).

The studies were analysed separately depending on whether they ensured that their control group was maintained at < 38 °C or included 38 °C within the 'normothermia' control range. Those studies that stated that they used controlled normothermia without specifying the temperature range were placed in the latter group. Studies that controlled temperature to < 38 °C showed no significant difference in mortality outcomes between the control group and the TH group (RR 1.01, 95% CI 0.82 to 1.32; $p = 0.73$). In contrast, in those studies that included 38 °C within the normothermia range, mortality was significantly higher in the control group (RR 0.61, 95% CI 0.44 to 0.87; $p = 0.005$).

Discussion

When the temperature of the control group was controlled (controlled normothermia) and fever was avoided, TH was no longer beneficial.

Conclusion

Overall, the results of this systematic review shed doubt on the outcome benefits of TH. Low-quality studies are more likely to show that TH improves mortality. In addition, this review highlights the importance of temperature management in the control group of TH trials and, in particular, the avoidance of fever.

Trial registration

This trial is registered as ISRCTN34555414.

Funding

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Chapter 1 Literature review: from bench to bedside

Background and objectives

This chapter provides a summary of the evidence that has supported the design of the Eurotherm3235 Trial.¹ This trial was a large, multinational, prospective, randomised controlled trial (RCT) of patients with raised intracranial pressure (ICP) after traumatic brain injury (TBI).

Traumatic brain injury is a major cause of death and severe disability throughout the world and leads to around 1 million hospital admissions per annum throughout the European Union (EU). It causes the majority of the 50,000 deaths from road traffic accidents each year and leaves 10,000 patients severely disabled; three-quarters of these victims are young people.² Additionally, TBI results in 290,000 hospital admissions and 51,000 deaths and leaves 80,000 patients with permanent neurological disabilities in the USA annually.³ The consequence of TBI is both a devastating emotional and physical impact and an enormous financial burden.⁴

Therapeutic hypothermia (TH) has been shown to improve outcome after cardiac arrest;⁴ therefore, both the European Resuscitation Council⁵ and the American Heart Association guidelines⁶ recommend the use of hypothermia in these patients. Hypothermia is also thought to improve neurological outcome after neonatal birth asphyxia.⁷ Cardiac arrest and neonatal asphyxia patient populations present to health-care services rapidly and without posing a diagnostic dilemma; therefore, systemic TH may be implemented relatively quickly. As a result of this, the use of hypothermia in these two populations is similar to the laboratory models in which systemic TH is commenced very soon after the injury and has shown so much promise.⁸

The need for resuscitation and computed tomography (CT) imaging to confirm the diagnosis in patients with TBI are factors that delay intervention with temperature reduction strategies. Treatments in TBI have traditionally focused on restoring and maintaining adequate brain perfusion, surgically evacuating large haematomas when necessary, and preventing or promptly treating oedema.⁴ Brain swelling can be monitored by measuring ICP, and in most centres ICP is used to guide treatments and to monitor their success. There is an absence of evidence for the five most commonly used treatments for raised ICP (hypertonics, sedation, muscle relaxants, barbiturates and decompressive craniectomy) and all are potential 'double-edged swords' with significant disadvantages. The use of hypothermia in patients with TBI may have beneficial effects in terms of both ICP reduction and possible neuroprotection.

Pathophysiology

Ischaemia has a key role in all forms of brain injury, and preventing ischaemic (or secondary) injury is at the core of all neuroprotective strategies.⁴ A complex cascade of processes ensues at the cellular level after a period of ischaemia, beginning from minutes to hours after injury and continuing for 72 hours or longer. Thus, there may be a window of opportunity of several hours, or even days, during which injury can be mitigated by treatments such as hypothermia.⁴

Early studies that used profound hypothermia in models of brain trauma used treatment paradigms that were not feasible in clinical practice.⁹ More recent studies have shown that moderate/mild hypothermia appears to be neuroprotective in well-characterised rodent models of TBI. The effects of systemic hypothermia (30–36 °C) following fluid percussion brain injury in rats were first investigated by Clifton *et al.*,¹⁰ who showed

that hypothermia of 33 °C resulted in reduced mortality rates and attenuated deficits in motor function and weight loss compared with normothermia. Dietrich *et al.*⁸ showed that post-traumatic hypothermia (30 °C) initiated 5 minutes after fluid percussion brain injury reduced overall contusion volume and preserved survival of the overlying cortical neurons. Therefore, these studies demonstrated that cooling after a TBI provided histological/cellular protection, improved motor and cognitive function and reduced mortality. Moderate hypothermia (30 °C), initiated 5 minutes after TBI, improved hippocampal-dependent learning and memory using the Morris water maze.¹¹ An important predictor of outcome in TBI patients, traumatic axonal pathology, is reduced with moderate post-injury hypothermia therapy.¹² Therefore, post-traumatic hypothermia modulates the major pathologies in TBI such as contusions, neuronal vulnerability and traumatic axonal injury. Mild hypothermia is therefore potentially attractive as a treatment for TBI as it modulates multiple mechanisms or pathways and has advantages over unipolar pharmacological attempts to provide neurological protection.

Blood–brain barrier

Alterations in blood–brain barrier (BBB) permeability after acute injury result in water, electrolytes, blood-borne substances and potential neurotoxic agents passing across the vascular system and into the brain parenchyma. Many studies have demonstrated the importance of brain and body temperature on the microvascular consequences of cerebral ischaemia and trauma. One study that assessed the effects of intra-ischaemic brain temperature (mild hypothermia) on the BBB found a reduction in extravasation of the protein tracer horseradish peroxidase.¹³ Brain water content is significantly reduced with hypothermia after focal cerebral ischaemia.^{14,15} This has been assessed in imaging studies, with magnetic resonance imaging finding that reductions in the apparent diffusion coefficient of water (cellular oedema) are also reduced by hypothermia.¹⁶

In models of post-traumatic injury, hypothermia has also been shown to reduce BBB permeability. Hypothermia may be attenuating BBB permeability by altering matrix metalloproteinases, which are critical extracellular enzymes that can disrupt the BBB.¹⁷ Given that BBB permeability, formation of vasogenic oedema and the extravasation of circulating inflammatory cells can adversely affect post-injury outcome, the effects of hypothermia are an important underlying mechanism for the beneficial effects of hypothermia.

Inflammation and oedema

The inflammatory response after TBI is significantly attenuated by hypothermia in laboratory and clinical studies. As well as attenuating the increase in BBB permeability and leucocyte margination, the endogenous inflammatory response of the central nervous system (CNS) is also reduced by hypothermia. Astrocytes and microglia respond to CNS injury by proliferating around the injury areas and releasing pro-inflammatory communication molecules as an endogenous repair mechanism. Hypothermia significantly attenuates the activation of both astrocytes and microglia.^{18–21} Combination therapy with the anti-inflammatory cytokine interleukin 10 (IL-10) and hypothermia therapy was attempted in both TBI and focal cerebral ischaemia.²² Synergistic effects were seen in focal cerebral ischaemia but not in TBI, suggesting that the cellular biology of inflammation in these two major CNS injuries has an influence on the effect of subsequent hypothermia.

Another major aspect of the inflammatory response to CNS injury is the release of reactive oxygen species by astrocytes and microglia. Hypothermia reduces increases in tissue levels of superoxide, nitric oxide and the hydroxyl radical.^{23,24} The level of the superoxide dismutase, the enzyme responsible for scavenging superoxide, is increased by hypothermia,^{25,26} and the level of the enzyme responsible for synthesising nitric oxide, nitric oxide synthase, is attenuated by hypothermia.²⁷

Metabolism

By exploiting local measures of glucose metabolism using 2-deoxyglucose techniques, researchers have shown that moderate hypothermia (30 °C) results in reduced glucose utilisation compared with normothermia.²⁸ Metabolic effects of mild hypothermia have also been demonstrated using nuclear magnetic resonance spectroscopy.²⁹ Therefore, hypothermia appears to lower metabolic and energy demands, which has potentially beneficial effects on cytoplasmic adenosine triphosphate (ATP) and

the maintenance of normal transmembrane ion and neurotransmitter gradients. The magnitude of preservation of ATP levels depends on both the temperature reduction and the severity of the injury. Therefore, an important mechanism for the neuroprotective effects of hypothermia is a reduction or delay in metabolic demand during and after an acute CNS injury.

Excitotoxicity

The effects of moderate hypothermia on glutamate excitotoxicity were reported using microdialysis to assay extracellular/extravascular concentrations of neurotransmitters after global ischaemia. A middle cerebral artery occlusion model is considered a reasonable model for haemorrhagic contusion. Busto *et al.*³⁰ showed that intra-ischaemic hypothermia (33 °C and 30 °C) attenuated the rise in extracellular levels of glutamate and dopamine after global cerebral ischaemia. These studies have been replicated in a variety of models of ischaemia, indicating that one of the major mechanisms by which temperature affects neuronal vulnerability is through reducing excitotoxicity following cerebral ischaemia.^{23,31,32} Delayed pharmacological treatments that reduce excitotoxicity further improve outcome in combination with hypothermia;³³ this may be a promising strategy for further studies. The glutamatergic receptors alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) are also modulated by hypothermia. Expression of hippocampal glutamate receptors is decreased after transient global ischaemia and this is completely blocked by intra-ischaemic hypothermia.³⁴

Other neurotransmitters are also modulated by hypothermia. Lyeth *et al.*³⁵ demonstrated that hypothermia (30 °C) reduced elevations in cerebrospinal levels of acetylcholine after TBI. Conversely, hypothermia delayed decreases in dopamine, noradrenaline and serotonin after global cerebral ischaemia.³⁶ However, other studies have demonstrated that hypothermia (32 °C) can improve outcome after CNS injury without attenuating extracellular levels of glutamate and aspartate.^{12,29,37} Although the neurotransmitter response in various injury models may be temperature dependent, attenuating other injury cascades may be more important in delivering possible beneficial effects of hypothermia.

Cerebrovascular effects

The effects of hypothermia on cerebral blood flow are controversial. In 1954, Rosomoff and Holaday³⁸ demonstrated that systemic hypothermia at 25 °C significantly lowered cerebral blood flow. However, in a model of selective brain cooling (30.9 °C), cortical blood flow measured by laser Doppler flowmetry was shown to increase above control levels.³⁹ Cerebrovascular changes secondary to cooling of the brain are important because reductions in blood flow to critical levels could have adverse effects on tissue survival and functional outcome.

Intracellular calcium-dependent signalling

There are pronounced changes in calcium-dependent intracellular signalling pathways after CNS injury. Normal neuronal activity is mediated by signalling through protein kinases and several of these have been documented to be disrupted by TBI and cerebral ischaemia. Temporary cerebral ischaemia inhibits the activity of calcium/calmodulin-dependent protein kinase II (CaMKII), a key protein kinase that mediates synaptic strength, and this is attenuated by hypothermia.⁴⁰ Protein kinase C (PKC) translocates to the membrane after cerebral ischaemia and undergoes inhibition; hypothermia rescues the inhibition of PKC activity and its translocation to the membrane.⁴¹ Recently, various transcription factors that participate in normal neuronal functioning have been shown to be sensitive to temperature. The immediate early gene *c-Fos*, which regulates key genetic responses of neurons, is activated by hypothermia after transient global ischaemia.^{18,42,43}

These studies suggest that temperature may have profound effects on events associated with neuronal injury as well as the normal processing of neuronal signals throughout brain circuits.

Neuronal cell death

Although neuronal necrosis is commonly seen in most CNS injury models, evidence for apoptotic cell death has also been documented using various histochemical and molecular techniques. As with necrosis, apoptotic cell death appears to be sensitive to post-injury hypothermic treatment strategies. Recent studies have indicated that apoptotic cell death is another important target by which temperature may affect long-term outcome in various models of CNS injury. Various gene families [genes with a similar sequence of deoxyribonucleic acid (DNA) nucleotides] have been shown to be sensitive to post-injury temperature manipulations in models of ischaemia and trauma.⁴⁴ The ability of post-injury temperature to affect the acute and more delayed genetic response to injury is important because these genes may play an important role in determining the cellular response(s) that results in secondary injury. Using high-throughput screening and bioinformatics, genomic studies are ongoing in many laboratories; these contemporary technologies will help to determine how hypothermia may protect, and potentially repair, CNS tissues after injury.

The Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies

The Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) group has a mission statement:

It is our contention that there is significant scope for improvements in the design, conduct, analysis and reporting of animal experiments. By minimising bias, such improvements would improve the amount of valid information gained from those animals used. By providing (using systematic review and meta-analysis) a precise and robust overview of existing data the need for further experiments, and the precise areas in which those experiments should focus, this approach would ensure that unnecessary replication did not occur. The proposed research is therefore crucial to the development of 'reduction' strategies.

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To date, this approach has not been rigorously applied to TBI models. Such an approach would enhance translational research and, hopefully, reduce futile clinical studies.

Therefore, with the proviso above, numerous animal experiments across different species have shown that induced hypothermia improves recovery outcome after experimental TBI. This has led to the undertaking of a large number of clinical trials.⁴ Interpretation of these results is complicated by the fact that these trials have enrolled different categories of patients, with different types of injuries, and have used widely diverging treatment protocols.⁴⁶ Most have used elevated ICP as an inclusion criterion, although some have used CT scan criteria. The duration of cooling has varied from 24 hours to > 5 days and rewarming rates have also varied. Some studies have used ICP to guide the depth and duration of treatment, although responses to rebound intracranial hypertension have differed.⁴ Use of co-interventions such as osmotic therapy, sedation, analgesia, paralysis and targets for mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) have also varied considerably.⁴ All of these factors can affect outcome after TBI in general and the potential efficacy of cooling in particular. Thus, interpreting, comparing and aggregating the results of these studies presents a number of complex challenges.

Review of clinical evidence

In total, 29 clinical studies have been performed to assess the effects of hypothermia in TBI.^{47–76} Twenty-seven of these were performed in adult patients, 18 of which included a control group. Data from one pilot study were subsequently included in a larger study, therefore leaving 17 studies. As outlined above, study protocols have differed considerably and not all studies were properly randomised.

Eighteen studies, with outcome data available for 2096 patients, used hypothermia in patients with high ICP that was refractory to 'conventional' treatments (usually sedation/analgesia, paralysis, osmotic therapy and sometimes barbiturates).^{58-61,63-71,73-77} All studies observed decreases in ICP during cooling. Thirteen of these studies reported significant improvements in outcome associated with hypothermia.^{58-61,63,65,67-71,74,77} All of these studies were performed in specialised neurotrauma centres with experience in applying hypothermia and managing its side effects. Ten were single-centre studies^{58-60,65,67,68,70,71,74,77} and three (all performed in China) were multicentre studies.^{61,63,69} Four additional studies observed a trend towards improved outcome, but these differences were not statistically significant.^{61,64,66,73}

In contrast, one of the two largest multicentre RCTs failed to show that induced hypothermia improved outcome at 6 months after TBI [poor outcome RR (risk ratio) 1, 95% CI (confidence interval) 0.8 to 1.2; $p = 0.99$].⁷⁶ The proportion of patients experiencing a poor outcome was significantly higher among those admitted to hospital with hypothermia who were randomised to normothermia and consequently rewarmed (78%, $n = 31$) than among the group admitted with hypothermia and treated with hypothermia (61%, $n = 38$) ($p = 0.09$).

On subsequent analysis, it became clear that, although this study was methodologically well designed, there was marked intercentre variance in the treatment effect of hypothermia, age of participants, severity of illness scoring between groups, management of intracranial hypertension and haemodynamic and fluid management.¹⁰ Induced hypothermia in the hypothermia group was started relatively late, with a slow speed of cooling (average time to target temperature > 8 hours) in all centres.

Hypotension (lasting > 2 hours) and hypovolaemia occurred three times more frequently in the hypothermia group than in the normothermia group. Bradycardia associated with hypotension also occurred four times more frequently in this group and electrolyte disorders and hyperglycaemia were also found more frequently in the hypothermia group⁷⁶ than in the normothermia group. All of these complications are known side effects of hypothermia. Most are easily preventable with good intensive care and should not be regarded as inevitable consequences of hypothermia treatment. As even very brief episodes of hypotension or hypovolaemia can adversely affect outcome in TBI, these and other issues may have significantly affected the results of this trial.^{10,78-80} One possible problem was that some of the participating centres had little or no previous experience in using hypothermia; large centres, familiar with cooling, showed apparently favourable neurological outcomes whereas smaller centres showed poor outcomes.

Induction of hypothermia

The most widely accepted use of hypothermia is after cardiac arrest. Two RCTs in this patient group found significant neurological improvements in patients whose initial cardiac rhythm was ventricular fibrillation or ventricular tachycardia and who were treated with hypothermia many hours after injury.^{81,82} Subsequent data from a large study of patients treated after myocardial infarction suggest that infarct size was reduced in patients who were cooled to < 35 °C before coronary intervention;⁸³ therefore, these studies suggest that faster cooling rates may be beneficial to patient outcome.

Methods of cooling can be broadly divided into two different techniques: surface cooling and core cooling.⁸⁴ The above study used surface cooling devices alone and found that a large number of patients did not reach the target temperature quickly enough before the start of the coronary intervention to demonstrate a benefit.⁸³ Despite advancing technology in surface cooling devices, and the introduction of endovascular catheters for core cooling, average periods of 2–3 hours are still required to reach temperatures of 32–34 °C.⁸⁴ The currently available surface cooling devices are also relatively large and cumbersome. This, coupled with the need for staff with specialist knowledge of the management of induced hypothermia, may prevent its use outside the intensive care unit (ICU).⁸⁴

One study has examined the feasibility, speed and complication rates of infusing refrigerated fluids intravenously to quickly induce hypothermia in patients with various neurological injuries.⁸⁴ The results showed that a 1500-ml infusion of 0.9% saline in patients without cardiogenic shock, administered over 30 minutes, reduced core temperature from 36.9 ± 1.9 °C to 34.6 ± 1.5 °C at 30 minutes and to 32.9 ± 0.9 °C at 60 minutes. Continuous monitoring of arterial blood pressure, heart rhythm, central venous pressure, arterial blood gases and serum levels of electrolytes, platelets and white blood cells showed no significant adverse events (AEs).⁸⁴

When hypothermia develops, the body will immediately try to counteract the temperature drop to maintain homeostasis.⁸⁵ One of the key mechanisms of heat production is shivering; this can lead to an increased oxygen consumption of 40–100%, which may be detrimental in this patient population. Sedation drugs are known to increase peripheral blood flow, which, in turn, will increase the transfer of heat from the core to the peripheries, thus reducing the core temperature.⁸⁵ Therefore, shivering may be counteracted by the administration of sedatives, anaesthetic agents, opiates and/or paralytic agents.⁸⁵

It should be noted, however, that the capacity and effectiveness of the mechanisms of controlling body temperature decrease with age. Younger patients will therefore react earlier, and with greater intensity, than older patients. For this reason, induction of hypothermia in younger patients often requires high doses of sedation drugs to neutralise the counter-regulatory mechanisms.⁸⁵

Together with TH therapy, all patients in the intervention group continued to be treated with stage 1 and 2 therapies as required to reduce intracranial hypertension.^{86,87} If raised ICP became resistant to these therapies, even when the depth of hypothermia was increased, then care was escalated to include stage 3 interventions. If this was required, TH treatment could be terminated for patients allocated to the treatment group and the patients rewarmed using the rewarming guideline. The reason for treatment escalation was then documented on the daily data collection form.

Meta-analyses

Six meta-analyses were published between 2002 and 2008.^{86–91} These included various numbers of trials with varying quality of randomisation and blinding procedures. All found a trend towards positive effects of hypothermia on neurological outcome, although statistical significance was reached in only two reviews (improved neurological outcome: RR 0.78, 95% CI 0.63 to 0.98;⁸⁶ RR 0.68, 95% CI 0.52 to 0.89⁸⁷).

The most recent meta-analysis⁹¹ included eight trials that studied comparable patient groups at baseline. Hypothermia was shown to reduce mortality by 20%, although this finding was not statistically significant (RR 0.80, 95% CI 0.59 to 1.09). Subgroup analysis showed that this effect was most significant when hypothermia was maintained for > 48 hours (RR 0.51, 95% CI 0.33 to 0.79). Hypothermia was also associated with a non-significant increase of 25% in neurological outcome when measured by the Glasgow Outcome Scale (GOS) at 6 months (RR 1.25, 95% CI 0.96 to 1.62). Despite not reaching statistical significance, the results showed an increased likelihood of improved neurological outcome when cooling was maintained for > 48 hours (RR 1.91, 95% CI 1.28 to 2.85). Another key finding of this meta-analysis was that hypothermia was only of significant benefit to those patients who had not received barbiturate therapy (RR 0.58, 95% CI 0.40 to 0.85).

A criticism of these analyses is that most failed to take account of important differences in patient groups, such as the presence or absence of intracranial hypertension, and differences in treatment protocols, with the exception of the use of hypothermia. Only one differentiated between studies that enrolled patients with normal ICP and those that enrolled patients with intracranial hypertension; this study found no neurological improvement associated with hypothermia.⁹⁰ Only two assessed the effects of treatment duration and speed of rewarming,^{86,87} concluding that cooling for > 48 hours and rewarming rates of 24 hours, or 1 °C per 4 hours, were both key factors in reducing mortality (RR 0.70, 95% CI 0.56 to 0.87) and improving neurological outcome (RR 0.79, 95% CI 0.63 to 0.98).

In summary, the evidence from previous research shows that induced hypothermia may be effective in patients with severe TBI and intracranial hypertension, provided that the treatment is continued for long enough (between 48 hours and 5 days) and that patients are rewarmed slowly (1 °C per 4 hours). Experience with cooling also appears to be important if complications, which may outweigh the benefits of hypothermia, are to be avoided.

Rationale for the Eurotherm3235 Trial

One of the most harmful consequences of TBI is cell injury and cell death in the brain. When this occurs, it starts a complex sequence of harmful, and potentially irreversible, processes at the cellular level. These processes can cause swelling (oedema) in the brain. This swelling increases the pressure inside the head and makes the injury worse. Preventing cell injury and cell death is therefore an important part of treatment. Cell death can occur from minutes to hours after injury and the harmful effects can last for 72 hours or longer. Thus, there may be a window of opportunity of several hours, or even days, during which cell death can be prevented by treatments such as hypothermia. Hypothermia treatment lowers the patient's temperature to below normal, which has a potentially beneficial effect on a number of problems caused by injury to brain cells.

The evidence from previous research shows that hypothermia treatment may be an effective therapy to improve outcome in patients who have suffered a TBI. Many trials have been carried out in this patient group, but none has been large enough to prove whether or not hypothermia is effective in preventing further brain damage and reducing death and disability. The Eurotherm3235 Trial aimed to provide a clear answer to this question.

Chapter 2 Trial design

Specific trial objectives and hypotheses

The Eurotherm3235 Trial tested the efficacy of hypothermia to reduce ICP after TBI and the effect of hypothermia treatment on functional recovery at 6 months after injury compared with standard care alone.

Hypothesis

Patients treated with TH (32–35 °C) will have reduced morbidity and mortality rates compared with those receiving standard care alone after TBI.

Research questions

- Does TH (32–35 °C) reduce morbidity and mortality rates at 6 months after TBI as assessed by the Glasgow Outcome Scale – Extended (GOSE) questionnaire?
- Does TH (32–35 °C) reduce intracranial hypertension?
- Is TH a cost-effective treatment to improve outcome after TBI?

Methods

Trial design

This was a pragmatic, multicentre RCT to examine the effects of hypothermia (32–35 °C) on outcome after TBI. Participants were randomised to receive either standard care alone or standard care with the addition of TH (*Figure 1*).

The experience from previous hypothermia trials underscores the potential difficulties in using TH treatment for TBI.¹⁰ For this reason, and to reduce intercentre variance, only centres experienced in the care of TBI patients and the use of hypothermia in this patient group were initiated.

At the time of designing the trial protocol in 2008, previous studies had found that TH lasting for at least 48 hours showed a trend towards reduced mortality and improved neurological function after TBI.⁹¹ Hypothermia (32–35 °C) was therefore continued for at least 48 hours in the trial and for as long as was necessary to reduce and maintain ICP at < 20 mmHg. This ICP threshold was used because the Brain Trauma Foundation guidelines⁸⁶ define intracranial hypertension as an ICP of > 20 mmHg. When ICP was stable, patients were then slowly rewarmed at a rate of 0.25 °C per hour (1 °C per 4 hours).

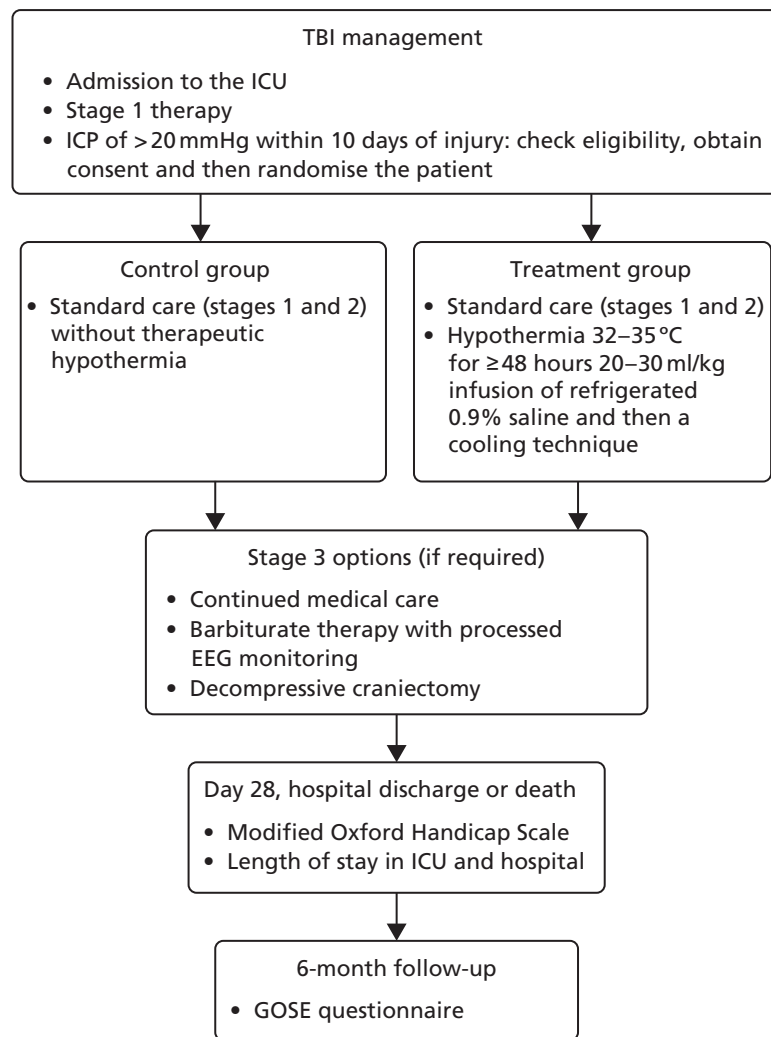


FIGURE 1 Study flow chart. EEG, electroencephalogram.

There are three recognised stages of TBI management (*Figure 2*).^{86,92}

Participants in the hypothermia group continued to be treated with stage 1 and 2 therapies as required to reduce intracranial hypertension.^{86,87} If raised ICP was resistant to these therapies, despite increasing the depth of hypothermia, care could be escalated to include stage 3 interventions.

During the preparation of the protocol, evidence suggested that patients were three times more likely to develop complications if hypothermia treatment was continued in conjunction with stage 3 interventions, that is, surgery or continuous infusion of barbiturates (the drugs used to treat ICP). Thus, we advised that the cooling intervention was withdrawn and the patient was rewarmed using the rewarming guideline as soon as it was safe to do so when the patient's care was escalated. The reason for treatment escalation was then documented on the daily data collection form.

The primary end point of the Eurotherm3235 Trial was the outcome 6 months after TBI using the GOSE questionnaire. Participants were sent the GOSE questionnaire with a covering letter by post 6 months after randomisation by the co-ordinating centre.

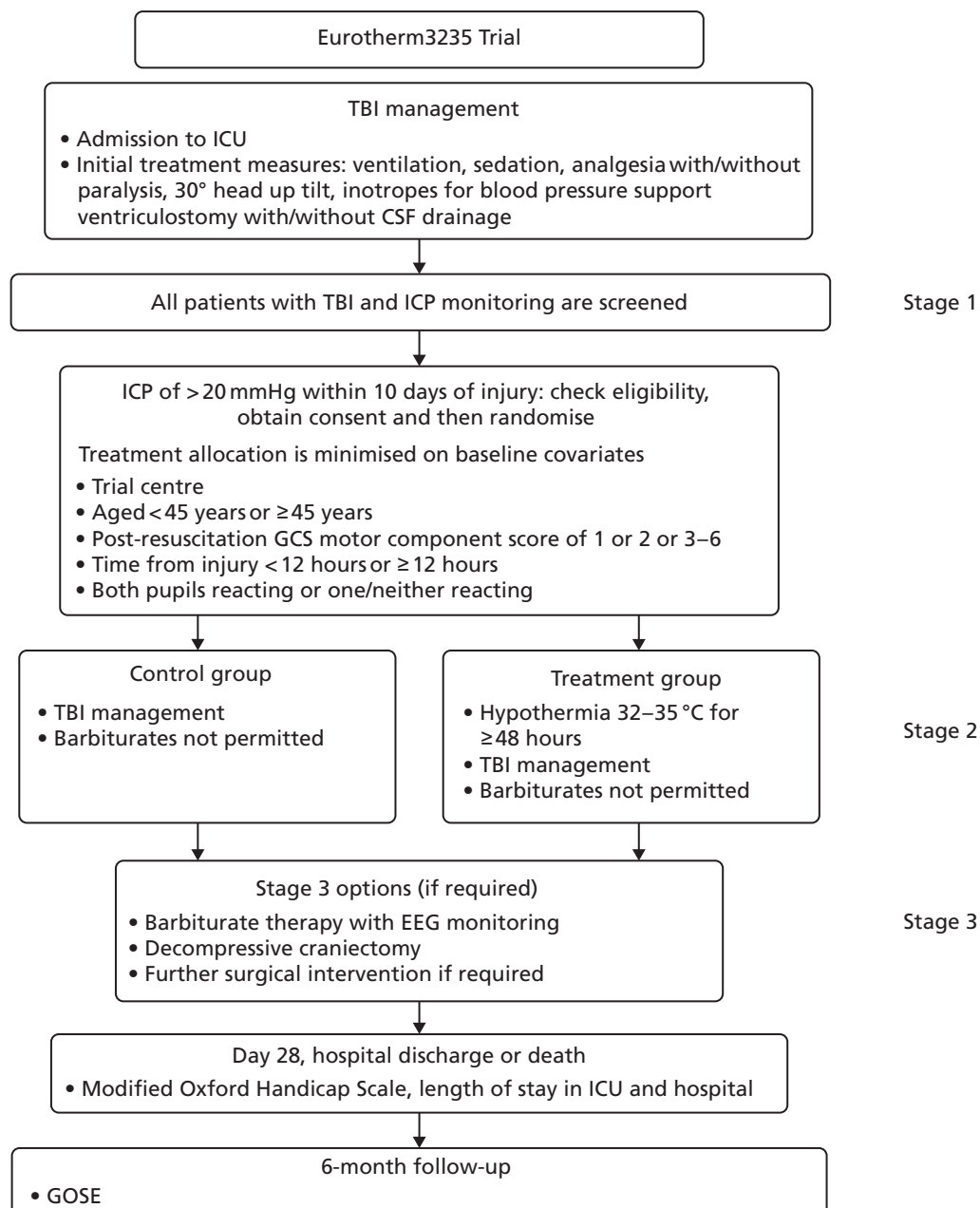


FIGURE 2 Three stages of ICP management after TBI. CSF, cerebrospinal fluid; EEG, electroencephalogram; GCS, Glasgow Coma Scale.

Important changes to methods after trial commencement

The inclusion criteria were changed in January 2012, based on the pilot phase findings,⁹³ to remove the upper age limit (previously 65 years) and increase the time from injury from 72 hours to 10 days. These changes provided important information on older patients and allowed patients with evolving brain swelling up to 10 days from injury to be included.

Participants

A total of 387 patients were recruited between January 2009 and October 2014.

The inclusion/exclusion criteria for the trial are given in the following sections.

Inclusion criteria

- Believed to be legal age to consent to take part in research.
- Primary closed TBI.
- Raised ICP of > 20 mmHg for ≥ 5 minutes after first-line treatments with no obvious reversible cause (e.g. patient position, coughing, inadequate sedation).
- ≤ 10 days from the initial head injury.
- Cooling device or technique available for > 48 hours.
- Core temperature of ≥ 36 °C (at the time of randomisation).
- An abnormal CT scan of the brain, defined as one that shows haematoma, contusion, swelling, herniation or compressed basal cisterns.

Exclusion criteria

- Patient already receiving TH treatment.
- Administration of barbiturate infusion prior to randomisation.
- Unlikely to survive for the next 24 hours in the opinion of the ICU consultant or consultant neurosurgeon treating the patient.
- Temperature of ≤ 34 °C at hospital admission.
- Pregnancy.

All female patients of childbearing age who met the inclusion criteria underwent a urine pregnancy test. This was performed by the investigator or research nurse in the ICU as part of the screening for eligibility procedure.

The Eurotherm3235 Trial enrolled patients after TBI who had an ICP of > 20 mmHg for ≥ 5 minutes, despite first-line treatments, with no obvious reversible cause, for example patient position, coughing or inadequate sedation. Although early cooling after injury is considered to be beneficial, this is offset by failure to show benefit from hypothermia in the absence of raised ICP. Enrolment to the Eurotherm3235 Trial was therefore allowed up to 10 days following injury.

The trial recruited incapacitated adult patients who were admitted to the neurological ICU. It was not possible to obtain consent from the patients before enrolment to the study as they were sedated and attached to a ventilator. Information booklets were therefore made available in the waiting area of the ICU and the patient's legal surrogate decision-maker, their next of kin/nearest relative/welfare guardian (in accordance with the laws of each country) was informed about the study by the ICU team soon after their relative was admitted. If they wanted further information about the trial or wished for their relative to participate, then the relative/welfare guardian contacted the researcher.

During this discussion, all stages of the trial were explained and the researcher explained that the patient may not have been eligible at that time, as they must have developed brain swelling before entering the study. Brain swelling can cause further brain damage if not treated quickly, so it was desirable that consent was obtained before any brain swelling occurred so that treatment could be allocated and started very soon after meeting the eligibility criteria. Patients who were consented early entered the study only if they developed brain swelling and met all the inclusion criteria for the trial at that time.

In accordance with the Good Clinical Practice guidelines,⁹⁴ the patient's nearest relative or welfare guardian was given the opportunity to ask questions and was given a copy of the trial information sheet to read and keep.

In some cases, the patient's nearest relative/welfare guardian was not present when the patient was admitted to the ICU. In usual circumstances, the health-care team contacted them to update them on the patient's condition soon after the patient was admitted. During this call, basic information was provided about the trial and they were asked if they would like more information. If further information was

requested, the local investigator or research nurse obtained telephone consent and followed this up with written consent as soon as possible afterwards.

Premature withdrawal

Participation in any research trial is voluntary; therefore, the participant or their legal representative was able to withdraw from the trial at any point. In this case, it was clearly documented on the premature withdrawal form whether or not any previously collected data could still be used in the analysis and which part of the trial the participant was being withdrawn from, using the following options:

1. withdraw entirely – the hypothermia intervention will be safely terminated, no further data will be collected and previously collected data will not be used in the analysis
2. withdraw entirely – the intervention will be safely terminated and no further data will be collected, but previously data collected may be used in the analysis
3. withdraw from the intervention but be willing to be followed up
4. withdraw from being followed up only.

Settings and locations where the data were collected

Induced hypothermia treatment is a specialist intervention; therefore, this study involved only neurological ICUs that were familiar with the use of hypothermia treatment in this patient group. Potential centres were asked to complete a centre survey that allowed the trial management team to assess the expertise at each centre before allowing a centre to take part.

A total of 61 specialist neurological ICUs were opened as recruiting centres across 18 countries between 2009 and 2015: Belgium ($n = 8$), England ($n = 21$), Estonia ($n = 1$), Germany ($n = 1$), Greece ($n = 6$), Hungary ($n = 1$), India ($n = 3$), Ireland ($n = 1$), Italy ($n = 5$), Northern Ireland ($n = 1$), the Netherlands ($n = 1$), Portugal ($n = 1$), Russia ($n = 1$), Saudi Arabia ($n = 1$), Scotland ($n = 3$), Spain ($n = 4$), Abu Dhabi ($n = 1$) and Wales ($n = 1$). Of these initiated centres, 54 centres screened patients and 46 centres randomised patients.

Once it was confirmed by the trial management team that a centre was eligible to participate, the process of obtaining ethics and hospital approvals varied between UK and non-UK centres. In the UK, ethics approval was obtained for the whole of the UK at the beginning of the trial, so that only hospital management approval was required for each new centre. To obtain this, the trial manager completed a site-specific information (SSI) form for each hospital and amended the consent documents to include the local hospital logos, contact details, etc. The trial manager then contacted the National Institute for Health Research Coordinated System for gaining NHS permission (NIHR CSP) network to ask for each hospital to be added to the list of participating centres. When this was approved, the local documents and SSI form were submitted to the local hospital research and development office for approval.

The process of obtaining approval in the non-UK centres was different as ethics approval was required for each hospital and the documents needed to be completed in the language of the country. For this reason, the local principal investigator (PI) had to complete the application form while the trial manager arranged for the trial documents to be translated into the appropriate language by an external translation company. The only exception to this was in Belgium, where the ethics process is centralised and, therefore, similar to that in the UK: one ethics application is submitted with a list of possible participating centres. When approval was given, each hospital submitted its own consent documents with its logo and contact details to its local hospital research office or independent review board for approval.

Trial site initiation visits

As soon as hospital approval was given for a site to participate in the trial, the trial manager contacted the PI and research team to arrange a site initiation visit. In the UK, the trial manager visited each site in person to conduct this visit. The visit lasted approximately 2 hours, during which time the staff were taught the

inclusion and exclusion criteria, the consenting process, how to randomise a patient, the trial interventions, how to complete the data collection forms on the internet-based electronic database, how to complete a serious adverse event (SAE) form and how to report a SAE. Staff were also given access to the test database to practise completing data input. Follow-up procedures were also discussed and staff were told about the importance of maintaining contact details for the participants and their nearest relative after discharge from the ICU. The procedure for withdrawing a participant from the trial if required was also discussed.

Site initiation visits for the non-UK sites

Owing to the variability of access to the non-UK sites, we developed an alternative method for site initiation in these centres. When it was feasible in terms of travel time, cost and language barrier, the trial manager visited each of the non-UK centres to carry out the trial initiation visit. When this was not feasible, the trial manager arranged a web conference with the PI and research team at each hospital. This meeting lasted for at least 2 hours and was conducted in English.

The countries that we visited were:

- Belgium – as the process of ethics approval was centralised for Belgian centres, we arranged a single site initiation meeting in Brussels and invited all centres to attend. Two additional centres joined the trial after this meeting. In this case, the trial manager arranged one meeting in one of the hospitals and both PIs and research staff from the two hospitals attended.
- Germany and Italy – because of the language barrier in two sites, we felt that the staff at these sites would benefit more from a face-to-face meeting rather than a teleconference.
- Republic of Ireland – the trial manager visited the site in Ireland as it was very similar to centres in the UK and was very easy to travel to.
- Portugal – a trial initiation meeting was possible at this site because the chief investigator was invited to attend the Portuguese Intensive Care Society meeting and so carried out the visit while attending the local conference.
- Spain – because of the language barrier in one site, we felt that the local staff would benefit more from a face-to-face meeting rather than a teleconference.

Once a site was initiated and activated on the database system, hospital staff could start to screen and recruit patients. Ongoing support was provided to the sites by the chief investigator and trial managers, either by e-mail or office telephone (available Monday–Friday, 09.00–17.00). We also set up a trial helpline using a separate mobile phone account, which was available out of hours and at weekends. The helpline was held by the chief investigator and trial managers on a rotational basis.

Interventions

Participants were randomised using minimisation criteria to either standard care (including ventilation, increased sedation and osmotherapy) or standard care with titrated TH (range 32–35 °C).

Prior to the induction of hypothermia, participants:

- were sedated and attached to a ventilator
- had probes inserted to monitor their blood pressure, fluid status and intracranial (brain) pressure
- had been assessed, including measurement of all laboratory values, by the doctor in charge of their care
- had continuous core body temperature monitoring in place using a probe in the pulmonary artery, oesophagus, bladder or rectum.

Hypothermia was then initiated with a bolus of 20–30 ml/kg of intravenous, refrigerated sodium chloride (0.9%) and maintained using each site's usual cooling technique. The core temperature was reduced by the minimum required to control ICP at ≤ 20 mmHg, within the limits of 32–35 °C. This ICP threshold was

used as intracranial hypertension is defined as an ICP of > 20 mmHg in the Brain Trauma Foundation guidelines.⁸⁶ If a participant's ICP was not controlled after cooling to 35 °C, then the temperature was incrementally decreased to a minimum temperature of 32 °C to control ICP.

Hypothermia was maintained for at least 48 hours and continued for as long as necessary to maintain ICP at < 20 mmHg. Rewarming was considered after 48 hours at a rate of 0.25 °C per hour provided ICP was ≤ 20 mmHg. The reason for this timeline was that previous studies have reported that TH that lasts for at least 48 hours showed a trend towards a reduction in mortality and improved neurological function after TBI.^{86,87,91}

A flow chart was designed for the induction and maintenance of TH in the intervention group (see *Appendix 1*). The depth of hypothermia (32–35 °C) was guided by ICP, with a higher pressure level warranting a cooler target temperature. A guideline was also designed for the detection and treatment of shivering (see *Appendix 2*). This was designed specifically for this trial, drawing on:

- the hospital protocol of the Mission Hospital, Orange County, CA, USA (permission given by Mary Kay Bader, Neuroclinical Nurse Specialist, Mission Hospital, Orange County, CA, USA)
- the hospital protocol of the University Medical Centre, Utrecht, the Netherlands (permission given by Dr Kees Polderman, University Medical Centre, Utrecht, the Netherlands)
- the Bedside Shivering Assessment Scale.⁹⁵

All participants in the intervention group also continued to be treated with stage 1 and 2 therapies as required to reduce intracranial hypertension.^{86,87} If ICP became resistant to these therapies, and despite increasing the depth of hypothermia, care was then escalated to include stage 3 interventions.

Evidence suggests, however, that a patient is three times more likely to develop complications if hypothermia treatment is given in conjunction with stage 3 interventions, namely surgery or the drugs used to treat severe brain swelling (known as barbiturates).⁹¹ If care was escalated, the participant was rewarmed using the rewarming guideline as soon as it was safe to do so. The reason for treatment escalation was then documented on the daily data collection form.

Outcomes

Primary

- Outcome at 6 months using the GOSE questionnaire.

Secondary

- Six-month mortality rate.
- Intracranial pressure control.
- Incidence of pneumonia across both groups.
- Length of stay in the ICU and hospital.
- Modified Oxford Handicap Scale score at 1 month, discharge from the randomising hospital or death, whichever took place first.
- Correlation between the predicted outcome using the MOHS score at hospital discharge and the predicted outcomes using the GOSE score at 6 months post injury.
- Health economics.

Primary end-point data collection

- Outcome at 6 months using the GOSE questionnaire.

To collect this information, a questionnaire was sent to all participants 6 months after injury.

This study recruited a very challenging patient group; patients who have suffered a head injury can have personality changes after the injury, which can make it challenging to follow them up. Therefore, drawing on our previous experience of the follow-up of brain-injured patients who had been admitted to the ICU, we knew that it was unlikely that all patients would be able to complete and return the questionnaire by themselves. Depending on the severity of their injury, many patients would still be in hospital at the 6-month follow-up. For this reason, we designed the follow-up procedures very carefully and included these processes in the initial consenting discussion.

At the same time as sending the questionnaire to participants at 6 months, we also sent a letter to those who gave consent for participants to enter the study. This letter informed them that the questionnaire had been sent to participants and asked them to help with completion of the questionnaire.

This procedure was discussed with those giving consent at the time of providing consent for a patient to enter the study. This procedure was also discussed with patients at the time of obtaining their subsequent consent (if applicable).

The procedures for the follow-up of participants varied between those who were recruited in the UK and those who were recruited in non-UK centres.

Follow-up procedure for UK centres

The first process for follow-up, before we sent anything to participants, was for the trial manager to ask the research nurse at each participant's centre to check the participant's vital status by determining whether the participant was still an inpatient or had been transferred to a rehabilitation centre. If the participant had been discharged home, the research nurse was then asked to contact the participant's GP to find out their vital status.

A GOSE questionnaire was then sent by post from the trial office in Edinburgh to all surviving participants 6 months after injury. At this time, we also sent a letter to those who gave consent for participants to enter the study, asking them to help with completion of the questionnaire.

In the pilot stage of the trial, if we did not receive a response from a participant within 3 weeks, we sent a shorter GOS questionnaire to the participant by post. If this was not returned after 2 weeks, then an independent and blinded researcher based in Edinburgh telephoned the participant to complete the short questionnaire with them over the telephone. The steps taken if a participant could not be contacted at this time varied depending on whether or not the participant had regained capacity and had given subsequent consent themselves:

- If the participant had regained capacity and had given retrospective consent, then the process ended here and the participant was documented as lost to follow-up.
- If the participant had not regained capacity and had not given follow-on consent, then the independent researcher telephoned the person who had given consent and asked them to complete the short questionnaire over the telephone.

This process was streamlined at the beginning of the main phase of the trial in January 2012. At this time, we decided to remove the process of sending the shorter questionnaire to participants and instead moved straight to telephoning participants if the first GOSE questionnaire was not returned after 3 weeks. In this case, the independent/blinded researcher based in Edinburgh telephoned participants if they had been discharged from hospital and completed the longer GOSE questionnaire with them over the telephone. If a participant was still in hospital and had not regained capacity to give follow-on consent, then the independent researcher telephoned the person who gave consent for the participant to enter the study and completed the longer GOSE questionnaire with them over the telephone.

Follow-up procedure for non-UK centres

Owing to the language barrier in the participating non-UK centres, it was not possible for the independent/blinded researcher in Edinburgh to contact the non-UK patients for follow-up. We therefore devised a slightly different process for the non-UK centres depending on their local procedures.

The procedure for follow-up was specifically outlined and discussed by the trial manager at the trial initiation meeting with the PI and research team at each of the non-UK centres.

Each PI was asked to identify someone in their hospital who would be blind to the participants' intervention and could carry out the follow-up. All centres, except those in Belgium, had an independent person at their hospital who carried out the follow-up over the telephone at 6 months. Belgium had a similar procedure to that in the UK in that a letter was sent to both the participant and the person who gave consent at 6 months and, if this was not returned after 3 weeks, an independent person at the centre contacted the participant by telephone and completed the longer GOSE questionnaire with them over the telephone.

Secondary end-point data collection

Data collection for the secondary end points comprised:

- intracranial pressure control
- incidence of pneumonia across both groups
- length of stay in the ICU and hospital
- Modified Oxford Handicap Scale score at 1 month, discharge from the randomising hospital or death, whichever took place first, collected using the daily data collection forms that were completed by the research team at each centre
- correlation between the predicted outcome using the MOHS score at hospital discharge and the predicted outcome using the GOSE score at 6 months post injury; this correlation was conducted by the trial statistician during the final analysis of the data
- health economics.

Owing to the unexpected result of the trial, with a higher rate of poor outcome in the hypothermia group, a health economic analysis was not deemed to be necessary.

Any changes to trial outcomes after the trial commenced, with reasons

No changes were made to the trial outcomes after commencement of the trial.

Sample size

The main evidence for the sample size calculation was the six meta-analyses published between 2002 and 2008.⁸⁶⁻⁹¹ These included varying numbers of clinical trials and examined each trial based on an assessment of the quality of randomisation and blinding procedures. All meta-analyses found a trend towards positive effects of hypothermia on neurological outcome, but statistical significance was reached in only two.^{86,87}

With a conventional dichotomous analysis of the GOSE, comparing the proportions of participants with an unfavourable outcome in the two groups, a 600-patient trial had 81% power at the 5% significance level (two-sided) to detect an absolute reduction of 12% (60% reducing to 48%). There was 87% power to detect an absolute reduction of 13% (60% reducing to 47%).

These calculations are conservative compared with the Peterson *et al.*⁹¹ systematic review of optimised therapeutic cooling.

Using an ordinal analysis of the GOSE together with covariate adjustment, there was the potential to increase the statistical efficiency of the analysis. If we achieve the efficiency gains suggested by simulations run by the IMPACT (International Mission on Prognosis and Clinical Trial Design in Traumatic Brain Injury) investigators⁹⁶ and demonstrated in a reanalysis of the CRASH (Corticosteroid Randomisation After Significant Head Injury) trial,⁹⁷ then a trial of 600 patients would have equivalent power to a trial of 1000 patients. This would give 80% power at the 5% significance level (two-sided) to detect an absolute reduction of 9% (60% reducing to 51%).

Data monitoring

The trial did not include any predefined interim analyses. The trial Data and Safety Monitoring Committee (DSMC) met regularly, however, to discuss the unblinded trial data and monitor the progress of the trial.

This committee was assembled using the Medical Research Council (MRC) guidelines for the development of a Data Monitoring and Ethics Committee (DMEC) and comprised three members:

- an expert clinician in intensive care (chairperson)
- an expert trial statistician
- an expert trialist.

A DSMC charter was developed and agreed by all members at the first DSMC meeting in 2010 (see *Appendix 3*). This charter included the guidelines for early termination, the quorum for decision-making and the reporting of the DSMC recommendations.

Statistical guidelines for termination: Data and Safety Monitoring Committee charter

The DSMC has the responsibility for deciding whether, while randomisation is in progress, the unblinded results (or the unblinded results for a particular subgroup) should be revealed to the Trial Steering Committee.

The DSMC terms of reference stated that it would do this if, and only if, two conditions were satisfied:

1. The blinded results provide proof beyond reasonable doubt that treatment is, on balance, either definitely harmful or definitely favourable for all, or for a particular category of, patients in terms of the major outcome.
2. The blinded results would, if revealed, be expected to substantially change the prescribing patterns of doctors who are already familiar with any other trial results that exist.

Exact criteria for 'proof beyond reasonable doubt' are not, and cannot be, specified by a purely mathematical stopping rule, but they are strongly influenced by such rules. DSMC members expressed sympathy with the stopping rule proposed in Part I of the 1976 report to the MRC Leukaemia Committee,⁹⁸ whereby an interim analysis of major end points would generally need to involve a difference between treatment and control of at least three standard errors to justify premature disclosure. An interim subgroup analysis would, of course, have to be even more extreme to justify disclosure. This rule has the advantage that the exact number and timing of interim analyses need not be prespecified. In summary, the stopping rules as specified in the CRASH trial protocol⁹⁹ (as successfully applied in other trials including the MRC International Stroke Trial,¹⁰⁰ which randomised 19,436 acute stroke patients) require extreme differences to justify premature disclosure and involve an appropriate combination of mathematical stopping rules and scientific judgement.

The DSMC met a total of nine times between February 2010 and October 2014. Of note is that the data showed a trend towards harm in the hypothermia group during the seventh and eighth DSMC meetings but the results did not become significant (difference of three standard errors) until the data were reviewed during the ninth meeting in October 2014.

At this time, the DSMC came to the following conclusions:

- There is no evidence of benefit for the patient group receiving the treatment to be evaluated.
- At best, a result of futility can be expected if the study is continued.
- There are signs of harm by the new treatment investigated including differences in mortality rate and a smaller number of patients achieving a relatively good outcome in the new treatment group, for those surviving the 6-month period after inclusion.

The DSMC therefore proposed that 'appropriate action is taken rapidly, as a consequence of the analysis done . . . in order to protect patients to be potentially included in this trial from now on' (abbreviated excerpt from the DSMC letter to the Trial Steering Committee).

This recommendation was sent to the chairperson of the Trial Steering Committee who convened an urgent Trial Steering Committee meeting. The meeting concluded that recruitment to the trial should be stopped early on the basis of futility and possible harm to participants. Recruitment was therefore stopped on 14 October 2014.

Randomisation

The randomisation of participants to either the hypothermia or the standard-care group was undertaken using a central internet-based randomisation service provided by Lincoln (Paris, France).

Type of randomisation

Participant allocation to either the hypothermia or the standard-care group by the online randomisation service used a minimisation technique with a random element using the following stratification variables:

- trial centre
- aged < 4–5 years or ≥ 45 years
- post-resuscitation Glasgow Coma Scale (GCS) motor component 1 or 2 or 3–6
- time from injury of < 12 hours or ≥ 12 hours
- pupils – both reacting or one or neither reacting
- allocation concealment mechanism.

It was not possible to conceal the allocated group from local investigators and study teams as it was clinically obvious which participants were receiving hypothermia, for example from the equipment required, participant temperature, blood results and fluid requirements.

To overcome potential bias, outcome data assessment were blinded.

Implementation

The central internet-based randomisation service provided by Lincoln generated the random allocation sequence (using minimisation with a random element) and assigned participants to groups.

Patients at each site were enrolled by either the PI or their deputy (e.g. research nurse or research doctor).

Blinding

It was not possible to blind local investigators, study teams or the participants' next of kin to group allocation as it was clinically obvious which participants were receiving hypothermia.

Outcome data assessment was blinded as the GOSE questionnaire was, in the first instance, posted to participants by the trial office in Edinburgh. If it was not returned in the post within 3 weeks, then an

independent researcher who was blind to treatment allocation telephoned the participant and/or their next of kin to complete the questionnaire with them over the telephone.

There were some similarities between interventions in the hypothermia group and interventions in the standard-care group of this trial. Both groups received stage 1 and stage 2 therapy (see *Figure 2*) throughout the trial period. It was also possible that participants in the standard-care group received temperature reduction, to a minimum of 36 °C, to treat fever using the same cooling technique as for participants in the hypothermia group. If this was required, the centres followed their local guidelines for fever management; no guidelines were provided as part of the trial.

Statistical methods

Overall statistical principles

The trial statistician performed the statistical programming and analysis to produce all summary tables and figures using the statistical package SAS® (version 9.2 or a more recent version; SAS Institute Inc., Cary, NC, USA; SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in the USA and other countries. ® indicates USA registration).

In general terms, categorical data are presented using counts and percentages, whereas continuous variables are presented using the mean, median, standard deviation (SD), minimum, maximum, interquartile points at 25% and 75% (Q1 and Q3) and number of participants with an observation (*n*). Data are split by time point when applicable.

All applicable statistical tests are two-sided and have been performed using a 5% significance level, leading to 95% (two-sided) CIs, unless otherwise specified.

Distributional assumptions underlying the statistical analyses are assessed by visual inspection of residual plots. Normality is examined by normal probability plots. If the distributional assumptions for the parametric approach were not satisfied, further data transformation (for achieving normality), or other suitable methods, were considered.

The intention-to-treat (ITT) and per-protocol (PP) populations are used to summarise all data and all analyses unless otherwise specified.

There has been no imputation of the data with regard to missing values or withdrawals for the statistical summaries and statistical analysis unless otherwise specified.

Statistical analysis plan

A detailed statistical analysis plan, setting out full details of the proposed analyses, was finalised before the trial database was locked for analysis.

As a result of the internal pilot phase,⁹³ the sample size for the full trial was reduced from 1800 to 600 participants. Two factors contributed to this decision:

1. The original sample size may have underestimated the possible benefit of hypothermia as, unlike participants in most previous hypothermia trials, participants in the Eurotherm3235 Trial had to have evidence of brain swelling (raised ICP of > 20 mmHg) to be eligible for randomisation.
2. We showed that an enhanced cooling intervention could be delivered, as described by Peterson *et al.*⁹¹

These data therefore informed the revised power calculation.

Population for analysis

Intention-to-treat population

The ITT population included all participants randomised into the Eurotherm3235 Trial. Participants were analysed in the group to which they were randomised, regardless of treatment received.

Per-protocol population

The PP population comprised those members of the ITT population who completed the study without a major protocol violation and who adequately complied with the administered treatment. Participants were analysed depending on the treatment that they actually received.

List of analyses

Recruitment and retention

No formal statistical testing was performed to look at recruitment and retention. A Consolidated Standards of Reporting Trials (CONSORT) flow chart is provided in *Chapter 3*. The numbers of participants screened, consented, randomised, treated, completed and discontinued by treatment and overall are also presented in *Chapter 3*. The number of participants discontinued early from the study is summarised by reason for withdrawal and treatment.

Baseline data: demographics and baseline/clinical characteristics

No formal statistical testing was performed. The following baseline characteristics are presented and summarised in the ITT report by treatment and overall (see *Chapter 3*):

- characteristic used in minimisation algorithm
- time from TBI to randomisation
- age and gender
- ICP, body temperature, post-resuscitation GCS and diagnosis details.

Protocol deviations/violations

No formal statistical testing was performed. All protocol deviations/violations are listed in the ITT statistical report (see *Chapter 3*).

Compliance with allocated treatment

Treatment compliance was determined using the following strategy:

- Step 1 – if a participant was allocated to a treatment then he or she should have received the allocated treatment.
- Step 2 – if a participant was allocated to the control then his or her core temperature should be $\geq 36^{\circ}\text{C}$ for all of the temperature observations for the first 48 hours from randomisation or until death (whichever event happens first).
- Step 3 – if a participant was allocated to the hypothermia group then his or her core temperature should strictly be $\geq 32^{\circ}\text{C}$ and $< 35^{\circ}\text{C}$ for all of the temperature observations from 4 hours after hypothermia started until the first 48 hours from randomisation or until death (whichever event happens first). Additionally, the participant could not have a barbiturate infusion within the first 48 hours from randomisation.

No formal statistical testing was performed. The number of treatment-compliant participants is summarised by treatment group as part of the ITT statistical report (see *Chapter 3*).

Primary outcome

Using an ordinal analysis of the GOSE scores, together with covariate adjustment (primary efficacy analysis), we were able to increase the statistical efficiency of the analysis^{101,102} so that a trial involving 600 participants would have power equivalent to that of a trial involving 1000 participants that assessed a binary outcome. We calculated that, with such an analysis, the study would have the equivalent of 80% power to detect a rate of unfavourable outcome (GOSE score of 1–4) that was 9 percentage points lower with hypothermia than with standard care (51% vs. 60%) at the 5% significance level (two-sided).

Data were analysed on an ITT basis. All randomised participants for whom outcome data were available were therefore included.

Participants were analysed depending on their allocated intervention, irrespective of whether or not their actual management complied with the allocated intervention.

The distributions of the 6-month GOSE scores between the two randomised groups (hypothermia vs. standard care) were compared using ordinal regression, adjusting for the following baseline covariates that were included in the minimisation algorithm:

- age (included as a continuous variable using a linear term in the regression model)
- post-resuscitation GCS motor component 1 or 2 compared with 3–6
- time from injury of < 12 hours compared with ≥ 12 hours
- pupils: both reacting compared with one reacting compared with neither reacting (included as an unordered categorical variable in the regression model).

As the covariates specified for the statistical analyses were required to inform the minimisation algorithm, there were no missing data for baseline covariates. A strenuous effort by the trial managers was also made to obtain complete outcome data at 6 months.

For this analysis, the eight-point GOSE was collapsed to six categories by pooling the 'death with vegetative state' and 'lower severe disability' categories. This was carried out to ensure that the analysis could not give 'credit' to an intervention that reduces mortality at the expense of increasing the proportion of severely disabled survivors.

The treatment effect was reported as an estimated adjusted common odds ratio (OR) with its corresponding 95% CI. The treatment groups are ordered in such a way that a common OR of < 1 corresponds to a benefit for hypothermia over standard care.

If there is strong evidence that the treatment effect does not satisfy the proportional odds assumption, which is required for the ordinal analysis, then this in itself will demonstrate that the distribution of the GOSE score differs between the two randomised groups. In such a situation, the distribution of the GOSE score in the two groups will be explored descriptively to give an insight into the nature of the treatment effect.

Sensitivity analyses

The unadjusted common OR and its corresponding 95% CI, derived by fitting an ordinal regression model with treatment as the only covariate included, is reported as a sensitivity analysis.

A binary logistic regression, using the same baseline covariates as set out in *List of analyses*, was also performed, using the conventional split of the GOSE as 'lower moderate disability' or better ('favourable') compared with 'upper severe disability' or worse ('unfavourable').

In a further exploratory analysis, the impact of missing outcome data was examined using an imputation technique, based on the simple IMPACT model⁹⁶ and the MOHS value and/or shorter GOS, if available, for imputing the missing GOSE data.

Secondary outcomes

The following outcome measures were tested for differences between the two treatment groups:

Six-month mortality rate

Survival from ICU admission to 6 months post randomisation (analysis of mortality) is presented using a Kaplan–Meier plot split by treatment group. The two survival curves have been compared formally using a log-rank test. If distributional assumptions hold, this will be analysed using Cox proportional hazards regression and the result presented as an estimated hazard ratio (HR) with its corresponding 95% CI.

Intracranial pressure control

The proportion of recorded ICP measurements of ≤ 20 mmHg were calculated for each participant. These proportions are summarised by treatment group in the ITT statistical report (see *Chapter 3*).

The effect of the intervention was estimated using a linear model adjusted by the minimisation variables. The effect of treatment allocation is reported as an adjusted mean difference with its corresponding 95% CI.

The above analysis was also repeated for an ICP of ≤ 25 mmHg as a sensitivity analysis.

Incidence of pneumonia across both groups

The number and proportion of participants who developed pneumonia were calculated by treatment group. The effect of the intervention was then estimated using binary logistic regression adjusted by minimisation variables. The effect of treatment allocation is reported as an adjusted OR with its corresponding 95% CI in the ITT statistical report (see *Chapter 3*).

Additionally, the first time (from day 3 to day 7) that pneumonia manifested is reported but statistical significance was not assessed.

Length of stay in the intensive care unit and hospital

The length-of-stay variables were calculated as follows:

- date/time from TBI (inclusion visit form) to randomisation
- date/time from randomisation to discharge from hospital (follow-up form)
- date/time from TBI (inclusion visit form) to discharge from hospital (follow-up form)
- studied ICU stay = date/time from randomisation to discharge from ICU (follow-up form)
- overall ICU stay = date/time of admission to ICU (inclusion visit form) to discharge from ICU (follow-up form)
- hospital stay = date/time from TBI (inclusion visit form) to discharge from hospital (follow-up form).

A linear regression model has been used to compare the mean lengths of stay between groups, adjusting by minimisation variables. The result are presented as an adjusted difference in mean length, together with its corresponding 95% CI, in the ITT statistical report (see *Chapter 3*).

Modified Oxford Handicap Scale score at 28 days, discharge from the randomising hospital or death, whichever took place first

This outcome was analysed as per the primary outcome using an adjusted ordinal regression. In this analysis, the six-point MOHS was collapsed to four categories by pooling 'death' with 'fully dependent, requiring attention day and night' and 'dependent, but not requiring constant attention'.

Correlation between the predicted outcome using the Modified Oxford Handicap Scale score at hospital discharge and the predicted outcome using the Glasgow Outcome Scale – Extended score at 6 months post injury

The Kendall tau-b correlation coefficient with its 95% CI between the MOHS score and the GOSE score is presented as part of the ITT statistical report (see *Chapter 3*).

A priori subgroups for the primary analysis were explored as follows:

- aged < 45 years compared with ≥ 45 years
- post-resuscitation GCS motor component 1 or 2 compared with 3–6
- time from injury of < 12 hours compared with ≥ 12 hours
- pupillary response: both or one reacting compared with none reacting
- UK centres compared with non-UK centres
- centres with high numbers of patients (i.e. 10 patients) compared with centres with low numbers (i.e. 10 patients).

These analyses were performed by including an interaction term between treatment and the relevant covariate in the ordinal regression model described above. A stricter level of statistical significance ($p < 0.01$) has been used in these analyses to reflect their exploratory nature.

Quality control of summary tables and statistical analysis

Isolated data errors, detected in the database as a result of the quality control checks, that were deemed significant were submitted for enquiry to the trial manager or designee.

Systematic data errors in the data reporting were investigated further; the data were corrected if necessary and the appropriate table was then rechecked.

Quality control/validation: summary tables

A random selection of unique analysis and summary tables was quality controlled using manual methods (e.g. comparison of results in the table with results calculated using a calculator, spreadsheet, database output or any alternative summarisation tool).

Quality control/validation: statistical analysis

Quality control/validation of statistical analyses was performed by peer review of program code, log and output. Additionally, the primary outcome analysis was replicated independently by a second statistician.

Unblinding procedures

Unblinding procedures were not applicable.

Chapter 3 Results

Results

Participant flow

Of the 2498 participants who were assessed for trial eligibility, 387 were randomly assigned, 386 received the intended treatment (after a withdrawal pre intervention) and 387 were analysed for the primary outcome (*Figure 3*). The most common reasons for exclusion from the trial were that ICP remained at ≤ 20 mmHg (41% of 2111 exclusions), the participant was unlikely to survive (8%) or the participant was already receiving hypothermia treatment (6%).

Recruitment

A total of 64 centres were initiated in 18 countries worldwide, with a target recruitment at each centre of four participants per year. A total of 387 participants were randomised from 47 of these centres between November 2009 (pilot phase from 10 January 2009 to 15 September 2011⁹³) and October 2014, when recruitment was stopped. Of these 387 participants, 53% ($n = 205$) were recruited in the UK. Follow-up ended 6 months after recruitment stopped, in April 2015.

Figure 4 shows the predicted versus actual recruitment throughout the trial.

Why the trial was ended

Recruitment was stopped in October 2014 when the Trial Steering Committee, in concurrence with the original recommendations of the DMEC, concluded that there were signs of harm with the induced hypothermia treatment and, at best, a result of futility would be expected if the trial were to continue. These findings were apparent when the study's designated primary outcome measure, analysed in accordance with the study's pre-stated statistical analysis plan, was examined.

Baseline data

On an ITT basis, a total of 195 participants were randomised to hypothermia and 192 participants were randomised to standard care. *Table 1* shows that there were no significant differences between groups in baseline characteristics.

Numbers analysed

Table 2 shows the breakdown of recruitment and treatment allocation by centre and *Table 3* shows the total number of participants screened and recruited at each centre.

The breakdown of participants recruited in the UK and non-UK centres was 53% and 47%, respectively.

Outcomes and estimation

All analyses were performed with SAS software. Analyses were performed on an ITT basis, incorporating all participants who underwent randomisation and for whom outcome data were available, with participants evaluated depending on their assigned intervention.

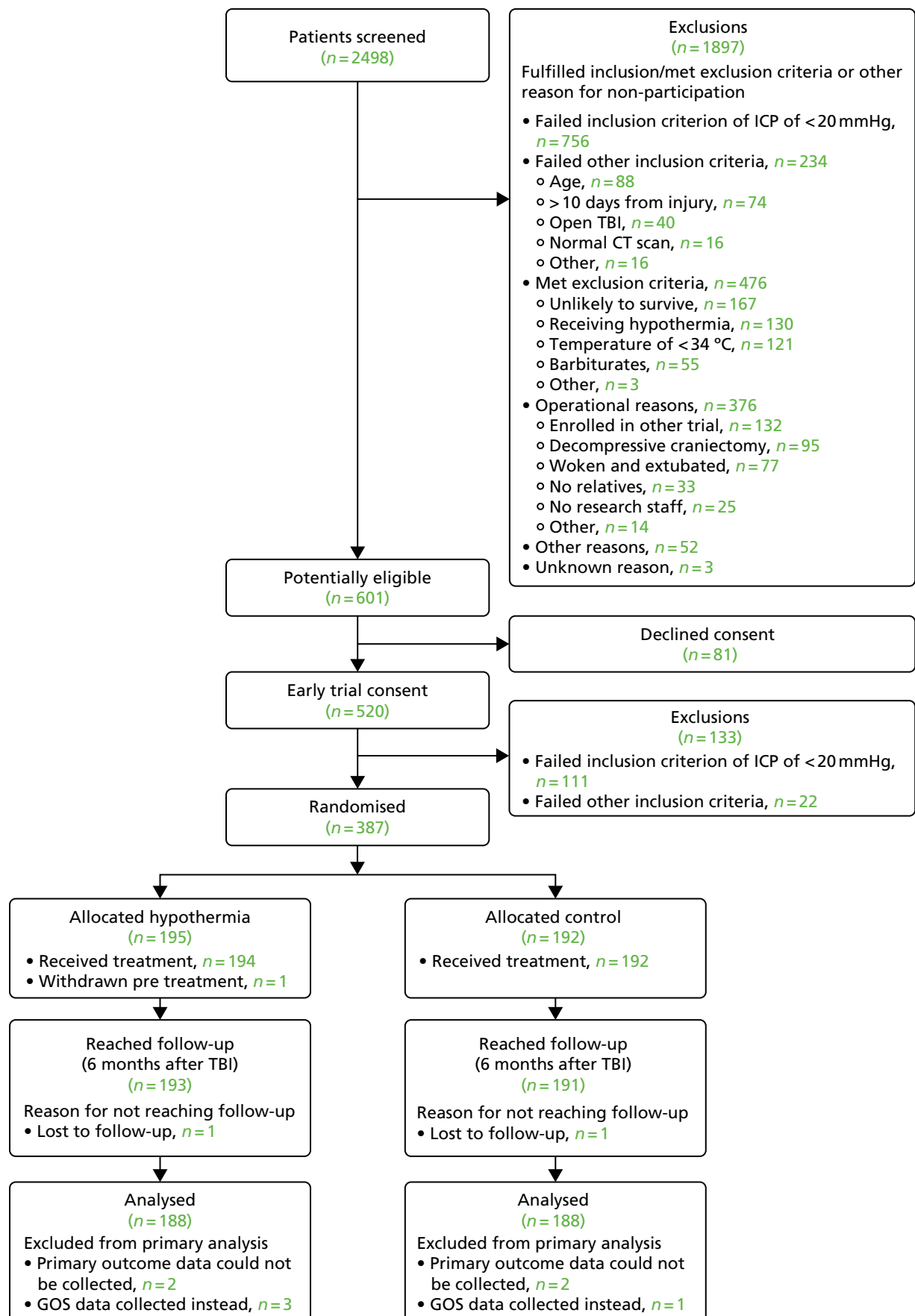


FIGURE 3 The CONSORT flow diagram. Adapted with permission from Andrews *et al.*¹ Copyright © (2015) Massachusetts Medical Society.

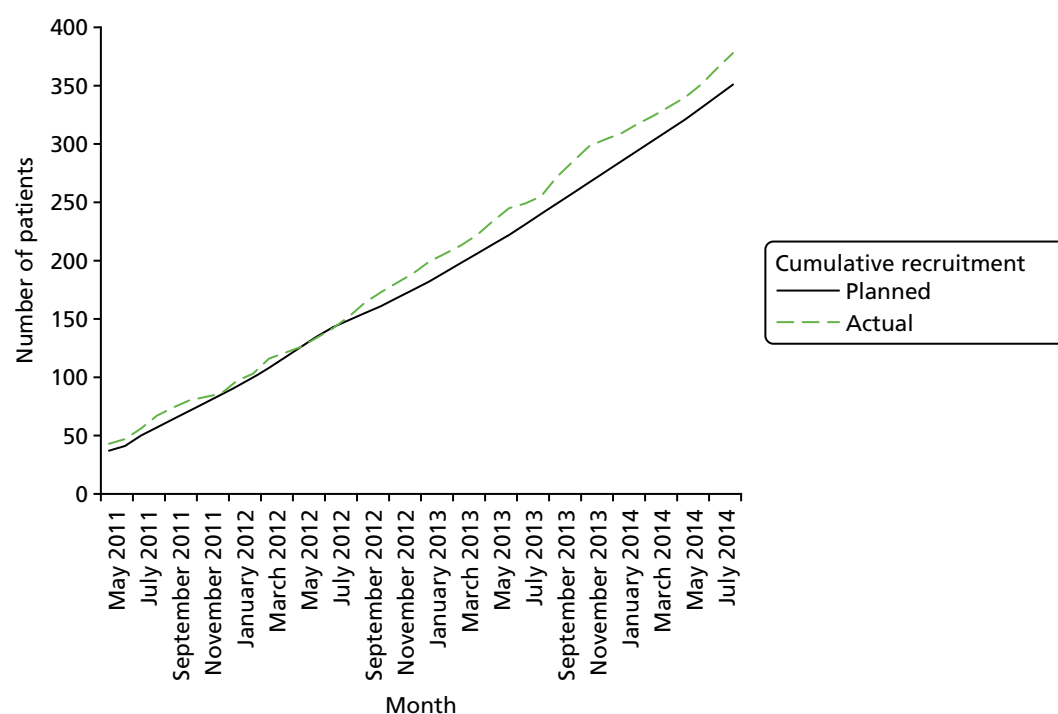


FIGURE 4 Recruitment graph. Adapted with permission from Andrews *et al.*¹ Copyright © (2015) Massachusetts Medical Society.

TABLE 1 Baseline demographic and clinical characteristics for each group. Adapted with permission from Andrews *et al.*¹ Copyright © (2015) Massachusetts Medical Society

| Demographic details | Treatment group | | Overall (<i>N</i> = 387) | <i>p</i> -value |
|--|----------------------------------|------------------------------|------------------------------|-----------------|
| | Hypothermia (<i>N</i> = 195) | Control (<i>N</i> = 192) | | |
| Exact age (years), mean (SD) | 37.4 (15.4) | 36.7 (14.9) | 37.0 (15.1) | 0.65 |
| Age compliance, <i>n</i> (%) | | | | |
| < 45 years | 131 (67.2) | 131 (68.2) | 262 (67.7) | |
| ≥ 45 years | 64 (32.8) | 61 (31.8) | 125 (32.3) | |
| Gender, <i>n</i> (%) | | | | |
| Male | 157 (80.5) | 164 (85.4) | 321 (82.9) | 0.20 |
| Female | 38 (19.5) | 28 (14.6) | 66 (17.1) | |
| Time from TBI (hours), mean (SD) | 77.96 (267.7) | 211.9 (1421.7) | 144.58 (1021.5) | 0.50 |
| Time from TBI compliance, <i>n</i> (%) | | | | |
| < 12 hours | 19 (9.7) | 15 (7.8) | 34 (8.8) | |
| ≥ 12 hours | 176 (90.3) | 177 (92.2) | 353 (91.2) | |
| ICP at randomisation (mmHg), mean (SD) | 25.2 (4.8) | 25.5 (6.4) | 25.3 (5.6) | 0.77 |
| Temperature at randomisation (°C), mean (SD) | 37.01 (0.7) | 37.10 (0.72) | 37.05 (0.7) | 0.19 |
| continued | | | | |

TABLE 1 Baseline demographic and clinical characteristics for each group. Adapted with permission from Andrews *et al.*¹ Copyright © (2015) Massachusetts Medical Society (*continued*)

| Demographic details | Treatment group | | Overall (<i>N</i> = 387) | <i>p</i> -value |
|---|----------------------------------|------------------------------|------------------------------|-----------------|
| | Hypothermia (<i>N</i> = 195) | Control (<i>N</i> = 192) | | |
| GCS eyes, ^a <i>n</i> (%) | | | | |
| None | 117 (60.0) | 113 (58.9) | 230 (59.4) | 0.96 |
| To pain | 17 (8.7) | 24 (12.5) | 41 (10.6) | |
| To sound | 29 (14.9) | 26 (13.5) | 55 (14.2) | |
| Spontaneous | 32 (16.4) | 29 (15.1) | 61 (15.8) | |
| GCS verbal, ^a <i>n</i> (%) | | | | |
| None | 109 (55.9) | 108 (56.3) | 217 (56.1) | 0.91 |
| Incomprehensible | 36 (18.5) | 35 (18.2) | 71 (18.3) | |
| Inappropriate | 21 (10.8) | 14 (7.3) | 35 (9.0) | |
| Confused | 21 (10.8) | 25 (13.0) | 46 (11.9) | |
| Orientated | 8 (4.1) | 10 (5.2) | 18 (4.7) | |
| GCS motor, ^a <i>n</i> (%) | | | | |
| None | 38 (19.5) | 38 (19.8) | 76 (19.6) | 0.61 |
| Extension | 18 (9.2) | 12 (6.3) | 30 (7.8) | |
| Abnormal flexion | 13 (6.7) | 18 (9.4) | 31 (8.0) | |
| Normal flexion | 22 (11.3) | 32 (16.7) | 54 (14.0) | |
| Localises | 70 (35.9) | 61 (31.8) | 131 (33.9) | |
| Obeys command | 34 (17.4) | 31 (16.1) | 65 (16.8) | |
| GCS sum (eyes + verbal + motor), <i>n</i> (%) | | | | |
| 3–8 | 125 (64.1) | 129 (67.2) | 254 (65.6) | 0.70 |
| 9–12 | 45 (23.1) | 34 (17.7) | 79 (20.4) | |
| 13–15 | 25 (12.8) | 29 (15.1) | 54 (14.0) | |
| Isolated TBI, <i>n</i> (%) | | | | |
| Yes | 123 (63.1) | 133 (69.3) | 256 (66.1) | 0.20 |
| No | 72 (36.9) | 59 (30.7) | 131 (33.9) | |
| Mechanism of injury, <i>n</i> (%) | | | | |
| Missing | 1 | 0 | 1 | 0.87 |
| Road traffic accident – pedestrian | 22 (11.3) | 31 (16.1) | 53 (13.7) | |
| Road traffic accident – motor vehicle | 68 (35.1) | 51 (26.6) | 119 (30.8) | |
| Push bike | 7 (3.6) | 10 (5.2) | 17 (4.4) | |
| Fall | 78 (40.2) | 78 (40.6) | 156 (40.4) | |
| Sports injury | 1 (0.5) | 1 (0.5) | 2 (0.5) | |
| Assault | 18 (9.3) | 21 (10.9) | 39 (10.1) | |

TABLE 1 Baseline demographic and clinical characteristics for each group. Adapted with permission from Andrews *et al.*¹ Copyright © (2015) Massachusetts Medical Society (*continued*)

| Demographic details | Treatment group | | Overall (<i>N</i> = 387) | <i>p</i> -value |
|---|----------------------------------|------------------------------|------------------------------|-----------------|
| | Hypothermia (<i>N</i> = 195) | Control (<i>N</i> = 192) | | |
| CT scan appearance – Marshall classification, ^b <i>n</i> (%) | | | | |
| Diffuse injury I ^c (no visible pathology) | 2 (1.0) | 0 | 2 (0.5) | 0.47 |
| Diffuse injury II ^d | 31 (15.9) | 36 (18.8) | 67 (17.3) | |
| Diffuse injury III ^e (swelling) | 39 (20.0) | 42 (21.9) | 81 (20.9) | |
| Diffuse injury IV ^f (shift) | 21 (10.8) | 15 (7.8) | 36 (9.3) | |
| Any lesion surgically removed | 46 (23.6) | 52 (27.1) | 98 (25.3) | |
| High- or mixed-density lesion | 56 (28.7) | 47 (24.5) | 103 (26.6) | |
| Any neurosurgery this admission, <i>n</i> (%) | | | | |
| Yes | 83 (42.6) | 73 (38.0) | 156 (40.3) | 0.36 |
| No | 112 (57.4) | 119 (62.0) | 231 (59.7) | |
| Number of neurosurgeries, <i>n</i> (%) | | | | |
| 0 | 112 (57.4) | 119 (62.0) | 231 (59.7) | 0.61 |
| 1 | 68 (34.9) | 51 (26.6) | 119 (30.7) | |
| 2 | 12 (6.2) | 18 (9.4) | 30 (7.8) | |
| 3 | 3 (1.5) | 4 (2.1) | 7 (1.8) | |

a GCS motor score was measured on hospital admission.

b The Marshall classification of TBI is based on a review of CT scans that were obtained at the screening visit. A diffuse injury indicates that no high-density or mixed-density lesions of > 25 mm³ are present.

c Diffuse injury I indicates no visible intracranial pathological features.

d Diffuse injury II indicates that cisterns are present with a midline shift of 0–5 mm or that lesion densities are present.

e Diffuse injury III indicates that cisterns are compressed or absent with a midline shift of 0–5 mm.

f Diffuse injury IV indicates a midline shift of ≥ 5 mm.

TABLE 2 Recruitment and treatment allocation by centre

| Trial centre | Treatment group, <i>n</i> (%) | | Overall, <i>n</i> (%) (<i>N</i> = 387) |
|---|----------------------------------|------------------------------|---|
| | Hypothermia (<i>N</i> = 195) | Control (<i>N</i> = 192) | |
| Western General Hospital, Edinburgh, UK | 24 (12.3) | 18 (9.4) | 42 (10.9) |
| Aberdeen Royal Infirmary, Aberdeen, UK | 2 (1.0) | 3 (1.6) | 5 (1.3) |
| Charing Cross Hospital, London, UK | 1 (0.5) | 2 (1.0) | 3 (0.8) |
| Derriford Hospital, Plymouth, UK | 9 (4.6) | 7 (3.6) | 16 (4.1) |
| Royal Berkshire Hospital, Reading, UK | 0 | 1 (0.5) | 1 (0.3) |
| Hull Royal Infirmary, Hull, UK | 2 (1.0) | 4 (2.1) | 6 (1.6) |
| Royal Hallamshire Hospital, Sheffield, UK | 2 (1.0) | 1 (0.5) | 3 (0.8) |
| University Hospital of North Staffordshire, UK | 6 (3.1) | 6 (3.1) | 12 (3.1) |
| Leeds General Infirmary, Leeds, UK | 2 (1.0) | 4 (2.1) | 6 (1.6) |
| Royal Victoria Infirmary, Newcastle upon Tyne, UK | 8 (4.1) | 4 (2.1) | 12 (3.1) |

continued

TABLE 2 Recruitment and treatment allocation by centre (*continued*)

| Trial centre | Treatment group, n (%) | | Overall, n (%) (N = 387) |
|--|--------------------------|----------------------|-----------------------------|
| | Hypothermia (N = 195) | Control (N = 192) | |
| North Estonia Medical Centre, Tallinn, Estonia | 7 (3.6) | 12 (6.3) | 19 (4.9) |
| Thriassio General Hospital of Eleusis, Magoula, Greece | 2 (1.0) | 3 (1.6) | 5 (1.3) |
| Albert Szent-Gyorgyi Medical Centre, Szeged, Hungary | 3 (1.5) | 2 (1.0) | 5 (1.3) |
| Hurstwood Park Neurological Centre, Haywards Heath, UK | 1 (0.5) | 0 | 1 (0.3) |
| Royal Victoria Hospital, Belfast, UK | 4 (2.1) | 3 (1.6) | 7 (1.8) |
| CHU de Charleroi, Charleroi, Belgium | 2 (1.0) | 2 (1.0) | 4 (1.0) |
| Evangelismos General Hospital, Athens, Greece | 1 (0.5) | 3 (1.6) | 4 (1.0) |
| Cliniques Universitaires UCL de Mont-Godinne, Dinant, France | 3 (1.5) | 2 (1.0) | 5 (1.3) |
| University Hospital Brussels, Brussels, Belgium | 2 (1.0) | 3 (1.6) | 5 (1.3) |
| CSL Clinique Saint Joseph, Arlon, Spain | 0 | 2 (1.0) | 2 (0.5) |
| CHR Citadelle, Liege, Belgium | 0 | 1 (0.5) | 1 (0.3) |
| St Mary's Hospital, London, UK | 3 (1.5) | 5 (2.6) | 8 (2.1) |
| King's College Hospital, London, UK | 14 (7.2) | 16 (8.3) | 30 (7.8) |
| Hôpital ERASME, Brussels, Belgium | 14 (7.2) | 13 (6.8) | 27 (7.0) |
| Istituto Clinico Humanitas, Milan, Italy | 3 (1.5) | 1 (0.5) | 4 (1.0) |
| Sklifosovsky Research Institute, Moscow, Russia | 1 (0.5) | 0 | 1 (0.3) |
| University Hospital of Ioannina, Ioannina, Greece | 0 | 1 (0.5) | 1 (0.3) |
| Cork University Hospital, Cork, Ireland | 6 (3.1) | 5 (2.6) | 11 (2.8) |
| University Hospital of Thessaly, Larissa | 5 (2.6) | 5 (2.6) | 10 (2.6) |
| BG Kliniken Bergmannstrost, Halle, Germany | 1 (0.5) | 1 (0.5) | 2 (0.5) |
| Salford Royal NHS Trust, Salford, UK | 8 (4.1) | 7 (3.6) | 15 (3.9) |
| Complejo Universitario de Burgos, Burgos, Spain | 6 (3.1) | 6 (3.1) | 12 (3.1) |
| University Hospital of Coventry and Warwickshire, Coventry, UK | 0 | 1 (0.5) | 1 (0.3) |
| Policlinico A. Gemelli, Rome, Italy | 2 (1.0) | 0 | 2 (0.5) |
| General Hospital of Kavala, Greece | 2 (1.0) | 0 | 2 (0.5) |
| Jai Prakash Narain Apex Trauma Centre, AIIMS, New Delhi, India | 20 (10.3) | 18 (9.4) | 38 (9.8) |
| University Hospital of Wales, UK | 9 (4.6) | 11 (5.7) | 20 (5.2) |
| Sheikh Khalifa Medical City, United Arab Emirates | 1 (0.5) | 1 (0.5) | 2 (0.5) |
| Erasmus University Medical Center, Rotterdam, the Netherlands | 4 (2.1) | 4 (2.1) | 8 (2.1) |
| UCIP, Hospital de Santo Antonio, Portugal | 1 (0.5) | 4 (2.1) | 5 (1.3) |
| Queen's Hospital, Romford, UK | 3 (1.5) | 1 (0.5) | 4 (1.0) |
| Royal London Hospital, UK | 3 (1.5) | 4 (2.1) | 7 (1.8) |
| Royal Preston Hospital, UK | 3 (1.5) | 2 (1.0) | 5 (1.3) |
| King Abdulaziz Medical City, Saudi Arabia | 2 (1.0) | 1 (0.5) | 3 (0.8) |
| Hospital Clinico San Carlos, Madrid, Spain | 1 (0.5) | 0 | 1 (0.3) |
| The Walton Centre, Liverpool, UK | 0 | 1 (0.5) | 1 (0.3) |

TABLE 3 Participant recruitment by centre and country

| Trial centre | Participants (n) | |
|--|------------------|----------|
| | Randomised | Screened |
| Western General Hospital, Edinburgh, UK | 42 | 137 |
| Jai Prakash Narain Apex Trauma Centre, AIIMS, New Delhi, India | 38 | 38 |
| King's College Hospital, London, UK | 30 | 144 |
| Hôpital Erasme, Brussels, Belgium | 27 | 27 |
| University Hospital of Wales, UK | 20 | 115 |
| North Estonia Medical Centre, Estonia | 19 | 107 |
| Derriford Hospital, Plymouth, UK | 16 | 143 |
| Salford Royal NHS Trust, UK | 15 | 155 |
| Royal Stoke University Hospital, UK | 12 | 127 |
| Royal Victoria Infirmary, Newcastle, UK | 12 | 112 |
| Complejo Universitario de Burgos, Spain | 12 | 25 |
| Cork University Hospital, Ireland | 11 | 58 |
| University Hospital of Thessaly, Larissa, Greece | 10 | 13 |
| St Mary's Hospital, London, UK | 8 | 157 |
| Erasmus University Medical Center, Rotterdam, the Netherlands | 8 | 81 |
| Royal Victoria Hospital, Belfast, UK | 7 | 98 |
| Royal London Hospital, UK | 7 | 142 |
| Leeds General Infirmary, UK | 6 | 83 |
| Hull Royal Infirmary, UK | 6 | 74 |
| Aberdeen Royal Infirmary, UK | 5 | 77 |
| Thriassio General Hospital of Eleusis, Attica, Greece | 5 | 43 |
| Albert Szent-Gyorgyi Medical Centre, Hungary | 5 | 7 |
| Cliniques Universitaires UCL de Mont Goddine, Belgium | 5 | 5 |
| UCIP Hospital de Santo António, Porto, Portugal | 5 | 8 |
| University Hospital Brussels, Belgium | 5 | 20 |
| Royal Preston Hospital, UK | 5 | 59 |
| CHU de Charleroi, Belgium | 4 | 10 |
| Evangelismos General Hospital, Greece | 4 | 22 |
| Istituto Clinico Humanitas, Milan, Italy | 4 | 9 |
| Queen's Hospital, Romford, UK | 4 | 31 |
| Charing Cross Hospital, London, UK | 3 | 23 |
| King Abdulaziz Medical City, Riyadh, Saudi Arabia | 3 | 35 |
| Royal Hallamshire Hospital, Sheffield, UK | 3 | 20 |
| G. Gennimatas General Hospital of Athens, Greece | 3 | 3 |
| Policlinico A. Gemelli, Rome, Italy | 2 | 11 |
| CSL Clinique St Joseph Arlon, Belgium | 2 | 11 |

continued

TABLE 3 Participant recruitment by centre and country (*continued*)

| Trial centre | Participants (n) | |
|--|------------------|----------|
| | Randomised | Screened |
| BG Kliniken Bergmannstrost, Halle, Germany | 2 | 12 |
| General Hospital of Kavala, Greece | 2 | 5 |
| Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates | 2 | 4 |
| Royal Berkshire Hospital, Reading, UK | 1 | 5 |
| Hurstwood Park Neurological Centre, Haywards Heath, UK | 1 | 31 |
| CHR Citadelle, Liège, Belgium | 1 | 2 |
| Sklifosovsky Research Institute, Moscow, Russia | 1 | 23 |
| University Hospital of Ioannina, Greece | 1 | 1 |
| University Hospital of Coventry and Warwickshire, UK | 1 | 115 |
| Hospital Clinico San Carlos, Madrid, Spain | 1 | 2 |
| The Walton Centre, Liverpool, UK | 1 | 1 |
| Ospedale San Gerardo di Monza, Italy | 0 | 15 |
| Medisch Centrum Haaglanden, the Netherlands | 0 | 11 |
| Hospital Germans Trias I Pujol, Badalona, Spain | 0 | 10 |
| University General Hospital of Alexandroupolis, Greece | 0 | 9 |
| Queen's Medical Centre, Nottingham, UK | 0 | 9 |
| Southern General Hospital, Glasgow, UK | 0 | 8 |
| St George's Hospital, London, UK | 0 | 3 |
| CHL-Apollo Hospitals, India | 0 | 2 |
| All centres | 387 | 2498 |

For the primary analysis, the distribution of the 6-month GOSE scores between the two groups (hypothermia vs. control) was compared with the use of ordinal logistic regression and with adjustment for the following baseline covariates:

- age (included as a continuous variable with the use of a linear term in the regression model)
- post-resuscitation GCS motor score [1 or 2 (no response or extensor response) vs. 3 to 6 (flexion or better response)]
- time from injury (< 12 hours vs. ≥ 12 hours)
- pupillary response (both reacting vs. one reacting vs. neither reacting; included as an unordered categorical variable in the regression model).

For this analysis, we collapsed the eight-point GOSE to six categories by pooling 'death with a vegetative state' and 'lower severe disability'. This ensured that the analysis would not favour an intervention that reduced mortality at the expense of increasing the proportion of severely disabled survivors. *Figure 5* shows the survival curves between groups.

Table 4 shows a detailed breakdown of the score category per group for both the full eight-point GOSE, the collapsed six-category GOSE and the dichotomised GOSE.

Table 5 shows the results of the primary analysis and primary subgroup analyses for the ITT population.

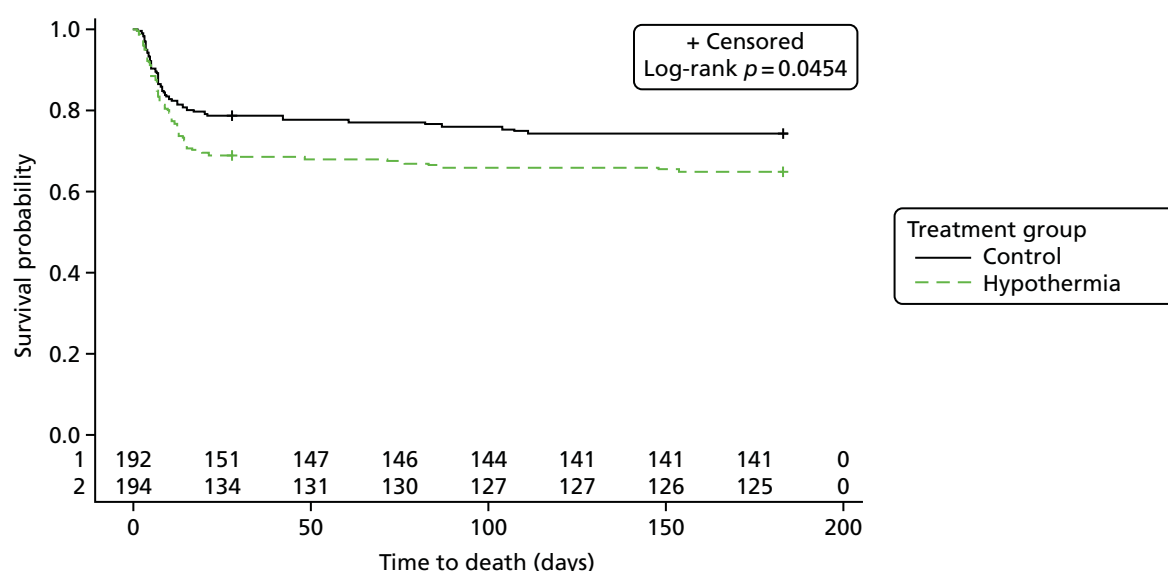


FIGURE 5 Kaplan–Meier survival curves per group.

TABLE 4 Detailed breakdown of the score category per group for both the full eight-point GOSE, the collapsed six-category GOSE and the dichotomised GOSE

| Parameter | Categories | Treatment group, n (%) | | Overall, n (%) |
|------------------------|---|------------------------|-------------------|----------------|
| | | Hypothermia (N = 195) | Control (N = 192) | |
| GOSE score at 6 months | Dead | 68 (34.9) | 51 (27.3) | 119 (31.7) |
| | Vegetative state | 0 | 3 (1.6) | 3 (0.8) |
| | Lower severe disability | 46 (24.5) | 43 (23.0) | 89 (23.7) |
| | Upper severe disability | 26 (13.8) | 21 (11.2) | 47 (12.5) |
| | Lower moderate disability | 16 (8.5) | 17 (9.1) | 33 (8.8) |
| | Upper moderate disability | 12 (6.4) | 15 (8.0) | 27 (7.2) |
| | Lower good recovery | 10 (5.3) | 20 (10.7) | 30 (8.0) |
| | Upper good recovery | 10 (5.3) | 17 (9.1) | 27 (7.2) |
| | GOSE score 2: vegetative state | 0 | 1 (0.5) | 1 (0.3) |
| | GOSE score 3: severe disability | 2 (1.0) | 1 (0.5) | 3 (0.8) |
| | GOSE score 4: moderate disability | 1 (0.5) | 0 | 1 (0.3) |
| | Lost to follow-up | 1 (0.5) | 1 (0.5) | 2 (0.5) |
| | Alive at follow-up, GOSE data not available | 2 (1.0) | 2 (1.0) | 4 (1.0) |
| | Withdrawn pre treatment | 1 (0.5) | 0 | 1 (0.3) |
| | GOSE score at 6 months: collapsed ^a | | | |
| | Dead, vegetative state, lower severe disability | 114 (60.6) | 98 (52.1) | 212 (56.4) |
| | Upper severe disability | 26 (13.8) | 21 (11.2) | 47 (12.5) |
| | Lower moderate disability | 16 (8.5) | 17 (9.0) | 33 (8.8) |
| | Upper moderate disability | 12 (6.4) | 15 (8.0) | 27 (7.2) |
| | Lower good recovery | 10 (5.3) | 20 (10.6) | 30 (8.0) |
| | Upper good recovery | 10 (5.3) | 17 (9.0) | 27 (7.2) |

continued

TABLE 4 Detailed breakdown of the score category per group for both the full eight-point GOSE, the collapsed six-category GOSE and the dichotomised GOSE (*continued*)

| Parameter | Categories | Treatment group, n (%) | | Overall, n (%) (N = 387) |
|--------------------------------------|--|--------------------------|----------------------|-----------------------------|
| | | Hypothermia (N = 195) | Control (N = 192) | |
| Dichotomised GOSE score ^a | Unfavourable: dead, vegetative state, lower severe disability, upper severe disability | 142 (74.3) | 120 (63.5) | 262 (68.9) |
| | Favourable: lower moderate disability, upper moderate disability, lower good recovery, upper good recovery | 49 (25.7) | 69 (36.5) | 118 (31.1) |

a These scores refer to the collapsed and dichotomised GOSE scores only.

TABLE 5 Results of the primary analysis (hypothermia vs. standard care) and primary subgroup analyses using the ITT population. Adapted with permission from Andrews *et al.*¹ Copyright © (2015) Massachusetts Medical Society

| Analysis | Estimate (95% CI) | p-value |
|--|---------------------|---------|
| Adjusted common OR ^a for GOSE score at 6 months ^{b,c} | 1.53 (1.02 to 2.30) | 0.04 |
| Adjusted OR ^a for unfavourable outcome ^{b,d} | 1.69 (1.06 to 2.70) | 0.03 |
| Treatment with hypothermia vs. control (unadjusted) | 1.53 (1.02 to 2.30) | 0.04 |
| Treatment with hypothermia vs. control (collapsed) | 1.55 (1.05 to 2.29) | 0.03 |
| Treatment with hypothermia vs. control (dichotomised) | 1.67 (1.06 to 2.70) | 0.027 |
| Subgroup analyses | | |
| Aged < 45 vs. ≥ 45 years ^d | 1.03 (1.01 to 1.04) | < 0.001 |
| Post-resuscitation GCS motor component [score of 1 or 2 (or no extension or response) vs. 3–6 (flexion or better response)] ^d | 0.23 (0.13 to 0.40) | < 0.001 |
| Time from injury (< 12 hours vs. ≥ 12 hours) ^d | 0.71 (0.35 to 1.44) | 0.34 |
| Pupillary response (both reacting vs. one reacting vs. neither reacting) ^d | 0.91 (0.36 to 2.31) | 0.0029 |

a An OR or common OR of < 1 corresponds to a benefit for hypothermia over control.

b Results were adjusted for age, post-resuscitation GCS motor score, time from injury and pupillary response.

c The eight-point GOSE was collapsed to six categories by pooling death (score of 1) with vegetative state (score of 2) and lower severe disability (score of 3).

d The eight-point GOSE was collapsed to two categories: favourable outcome (score of 5–8) and unfavourable outcome (score of 1–4).

The results of the primary analysis were unexpected and showed that participants in the hypothermia group had significantly poorer outcomes at 6 months ($p = 0.04$) and a higher mortality rate ($p = 0.05$) than those treated with standard care alone. Furthermore, the primary subgroup analysis showed that age and post-resuscitation GCS motor component were specifically linked to outcome; in this patient population, these findings would be expected.

Secondary analyses

Secondary outcomes of the trial were:

- 6-month mortality rate
- intracranial pressure control
- incidence of pneumonia across both groups
- length of stay in the ICU and hospital

- modified Oxford Handicap Scale score at 1 month, discharge from the randomising hospital or death, whichever took place first
- correlation between the predicted outcome using the MOHS at hospital discharge and the GOSE score at 6 months post injury
- health economics.

The results of the secondary end-point analyses are shown in *Table 6*.

The physiological measures detailed in *Table 5* are also shown as trends in *Figures 6 and 7*.

TABLE 6 Results of the secondary end-point analyses

| Analysis of secondary outcomes: hypothermia vs. control | Estimate (95% CI) | p-value |
|--|------------------------|---------|
| Unadjusted HR for death incidence between randomisation and 6 months | 1.45 (1.01 to 2.10) | 0.047 |
| Physiological measures ^a | | |
| Adjusted mean difference in ICP on days 1–7 (mmHg) | –0.48 (–2.04 to 1.08) | 0.55 |
| Adjusted mean difference in core temperature on days 1–7 (°C) | –2.14 (–2.34 to –1.94) | < 0.001 |
| Adjusted mean difference in MAP on days 1–7 (mmHg) | 1.20 (–0.46 to 2.86) | 0.16 |
| Adjusted mean difference in CPP on days 1–7 (mmHg) | 1.61 (–0.36 to 3.58) | 0.11 |
| Adjusted mean difference in squared proportion of ICP measurements of ≤ 20 mmHg on days 1–7 | 440 (–1.60 to 1000) | 0.47 |
| Incidence of patients who had presence of pneumonia on days 3–7 | 1.04 (0.69 to 1.58) | 0.84 |
| Adjusted mean difference in log-transformed length of ICU stay (log-hours) ^c | 0.05 (0.11 to 0.22) | 0.54 |
| Adjusted common OR ^b for MOHS grade at 28 days ^{c,d} | 1.65 (0.91 to 3.02) | 0.10 |

a Values were calculated with the use of a repeated-measures model adjusted for age, postresuscitation GCS motor score, time from injury, pupillary response, study day and (when available) baseline value. These are post hoc analyses.

b An OR or common OR of < 1 corresponds to a benefit for hypothermia over control.

c Results were adjusted for age, post-resuscitation GCS motor score, time from injury and pupillary response.

d The six grades of the MOHS were collapsed to four categories by pooling dependent, fully dependent and death.

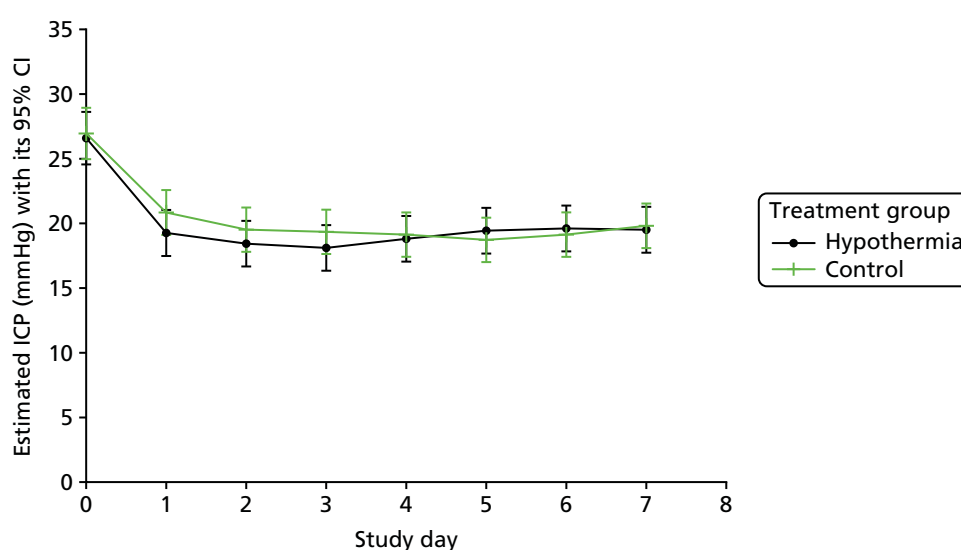


FIGURE 6 Intracranial pressure control per group. Adapted with permission from Andrews *et al.*¹ Copyright © (2015) Massachusetts Medical Society.

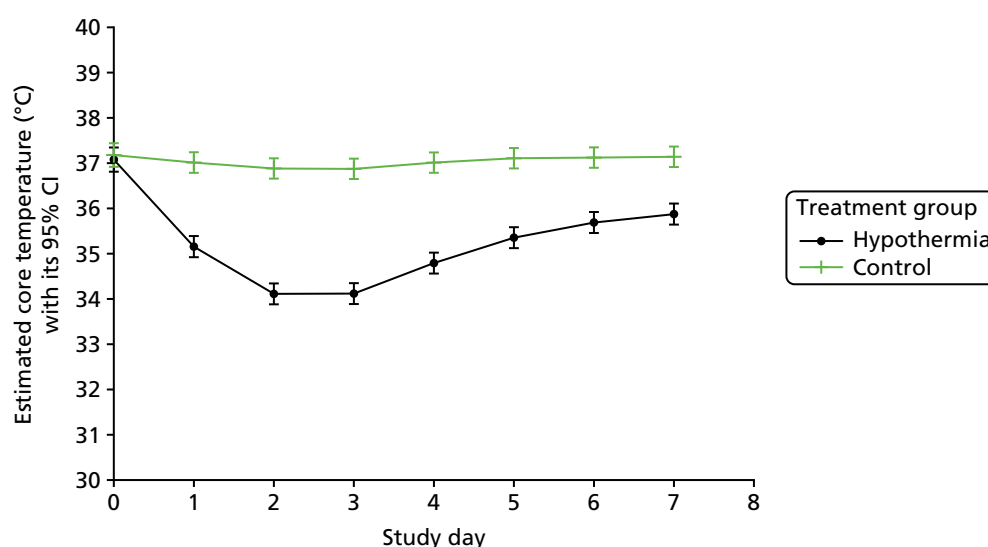


FIGURE 7 Temperature control per group. Adapted with permission from Andrews *et al.*¹ Copyright © (2015) Massachusetts Medical Society.

Per-protocol analysis

We also carried out a PP analysis. Participants from the ITT population were included in this analysis if they completed the study without a major protocol violation and adequately complied with the prescribed treatment group. Participants were analysed depending on the treatment they actually received. A total of 257 participants were included in this analysis: 125 in the hypothermia group and 132 in the control group.

Table 7 shows that, as with the ITT population (see Table 5), there were no significant differences in baseline characteristics in the PP population. Table 8 shows the breakdown of GOSE score category for the full eight-point GOSE, the collapsed six-point GOSE and the dichotomised GOSE in this population.

TABLE 7 Baseline demographic and clinical characteristics for each PP group

| Demographic details | Treatment group | | Overall (N = 257) | p-value |
|--|-----------------------|-------------------|-------------------|---------|
| | Hypothermia (N = 125) | Control (N = 132) | | |
| Exact age (years), mean (SD) | 38.3 (15.5) | 37.0 (15.0) | 37.6 (15.2) | 0.46 |
| Age compliance, n (%) | | | | |
| < 45 years | 83 (66.4) | 90 (68.2) | 173 (67.3) | 0.76 |
| ≥ 45 years | 42 (33.6) | 42 (31.8) | 84 (32.7) | |
| Gender, n (%) | | | | |
| Male | 98 (78.4) | 115 (87.1) | 213 (82.9) | 0.06 |
| Female | 27 (21.6) | 17 (12.9) | 44 (17.1) | |
| Time from TBI (hours), mean (SD) | 91.54 (332.71) | 264.68 (1315.76) | 180.82 (974.83) | 0.63 |
| Time from TBI compliance, n (%) | | | | |
| < 12 hours | 10 (8.0) | 8 (6.1) | 18 (7.0) | 0.02 |
| ≥ 12 hours | 115 (92.0) | 124 (93.9) | 239 (93.0) | |
| ICP at randomisation (mmHg), mean (SD) | 25.1 (4.8) | 25.1 (6.0) | 25.1 (5.5) | 0.86 |
| Temperature at randomisation (°C), mean (SD) | 37.01 (0.74) | 37.17 (0.67) | 37.09 (0.71) | 0.65 |

TABLE 7 Baseline demographic and clinical characteristics for each PP group (*continued*)

| Demographic details | Treatment group | | | p-value |
|--|-----------------------|-------------------|-------------------|---------|
| | Hypothermia (N = 125) | Control (N = 132) | Overall (N = 257) | |
| GCS eyes, ^a n (%) | | | | |
| None | 78 (62.4) | 76 (57.6) | 154 (59.9) | 0.39 |
| To pain | 10 (8.0) | 16 (12.1) | 26 (10.1) | |
| To sound | 23 (18.4) | 17 (12.9) | 40 (15.6) | |
| Spontaneous | 14 (11.2) | 23 (17.4) | 37 (14.4) | |
| GCS verbal, ^a n (%) | | | | |
| None | 67 (53.6) | 73 (55.3) | 140 (54.5) | 0.93 |
| Incomprehensible | 26 (20.8) | 24 (18.2) | 50 (19.5) | |
| Inappropriate | 13 (10.4) | 10 (7.6) | 23 (8.9) | |
| Confused | 16 (12.8) | 16 (12.1) | 32 (12.5) | |
| Orientated | 3 (2.4) | 9 (6.8) | 12 (4.7) | |
| GCS motor, ^a n (%) | | | | |
| None | 22 (17.6) | 25 (18.9) | 47 (18.3) | 0.67 |
| Extension | 10 (8.0) | 10 (7.6) | 20 (7.8) | |
| Abnormal flexion | 9 (7.2) | 10 (7.6) | 19 (7.4) | |
| Normal flexion | 17 (13.6) | 24 (18.2) | 41 (16.0) | |
| Localises | 48 (38.4) | 41 (31.1) | 89 (34.6) | |
| Obeys command | 19 (15.2) | 22 (16.7) | 41 (16.0) | |
| GCS sum (eyes + verbal + motor), n (%) | | | | |
| 3–8 | 82 (65.6) | 89 (67.4) | 171 (66.5) | 0.93 |
| 9–12 | 29 (23.2) | 20 (15.2) | 49 (19.1) | |
| 13–15 | 14 (11.2) | 23 (17.4) | 37 (14.4) | |
| Isolated TBI, n (%) | | | | |
| Yes | 74 (59.2) | 96 (72.7) | 170 (66.1) | 0.23 |
| No | 51 (40.8) | 36 (27.3) | 87 (33.9) | |
| Mechanism of injury, n (%) | | | | |
| Missing | 1 | 0 | 1 | 0.91 |
| Road traffic accident – pedestrian | 13 (10.5) | 19 (14.4) | 32 (12.5) | |
| Road traffic accident – motor vehicle | 46 (37.1) | 37 (28.0) | 83 (32.4) | |
| Push bike | 3 (2.4) | 8 (6.1) | 11 (4.3) | |
| Fall | 49 (39.5) | 54 (40.9) | 103 (40.2) | |
| Sports injury | 0 | 1 (0.8) | 1 (0.4) | |
| Assault | 13 (10.5) | 13 (9.8) | 26 (10.2) | |
| CT scan appearance – Marshall classification, ^b n (%) | | | | |
| Diffuse injury I ^c (no visible pathology) | 1 (0.8) | 0 | 1 (0.4) | 0.59 |
| Diffuse injury II ^d | 19 (15.2) | 27 (20.5) | 46 (17.9) | |
| Diffuse injury III ^e (swelling) | 21 (16.8) | 25 (18.9) | 46 (17.9) | |
| Diffuse injury IV ^f (shift) | 17 (13.6) | 10 (7.6) | 27 (10.5) | |
| Any lesion surgically removed | 37 (29.6) | 39 (29.5) | 76 (29.6) | |
| High- or mixed-density lesion | 30 (24.0) | 31 (23.5) | 61 (23.7) | |

continued

TABLE 7 Baseline demographic and clinical characteristics for each PP group (*continued*)

| Demographic details | Treatment group | | | p-value |
|--|-----------------------|-------------------|-------------------|---------|
| | Hypothermia (N = 125) | Control (N = 132) | Overall (N = 257) | |
| Any neurosurgery this admission, n (%) | | | | |
| Yes | 60 (48.0) | 52 (39.4) | 112 (43.6) | 0.16 |
| No | 65 (52.0) | 80 (60.6) | 145 (56.4) | |
| Number of neurosurgeries, n (%) | | | | |
| 0 | 65 (52.0) | 80 (60.6) | 145 (56.4) | |
| 1 | 49 (39.2) | 35 (26.5) | 83 (32.7) | |
| 2 | 8 (6.4) | 14 (10.6) | 22 (8.6) | |
| 3 | 3 (2.4) | 3 (2.3) | 6 (2.3) | |

a GCS motor score was measured on hospital admission.

b The Marshall classification of TBI is based on a review of CT scans that were obtained at the screening visit. A diffuse injury indicates that no high-density or mixed-density lesions of > 25 mm³ are present.

c Diffuse injury I indicates no visible intracranial pathologic features.

d Diffuse injury II indicates that cisterns are present with a midline shift of 0–5 mm or that lesion densities are present.

e Diffuse injury III indicates that cisterns are compressed or absent with a midline shift of 0–5 mm.

f Diffuse injury IV indicates a midline shift of > 5 mm.

TABLE 8 The outcome per group for the full eight-point GOSE, the collapsed six-category GOSE and the dichotomised GOSE in the PP population

| Parameter | Categories | Treatment group, n (%) | | |
|-----------------------------------|--|------------------------|-------------------|-------------------|
| | | Hypothermia (N = 125) | Control (N = 132) | Overall (N = 257) |
| GOSE score at 6 months | Dead | 41 (33.6) | 29 (22.7) | 70 (28.0) |
| | Vegetative state | 0 | 1 (0.8) | 1 (0.4) |
| | Lower severe disability | 30 (24.6) | 32 (25.0) | 62 (24.8) |
| | Upper severe disability | 16 (13.1) | 15 (11.7) | 31 (12.4) |
| | Lower moderate disability | 11 (9.0) | 9 (7.0) | 20 (8.0) |
| | Upper moderate disability | 10 (8.2) | 12 (9.4) | 22 (8.8) |
| | Lower good recovery | 6 (4.9) | 16 (12.5) | 22 (8.8) |
| | Upper good recovery | 8 (6.6) | 14 (10.9) | 22 (8.8) |
| GOSE score at 6 months: collapsed | Dead, vegetative state, lower severe disability | 71 (58.2) | 62 (48.4) | 133 (53.2) |
| | Upper severe disability | 16 (13.1) | 15 (11.7) | 31 (12.4) |
| | Lower moderate disability | 11 (9.0) | 9 (7.0) | 20 (8.0) |
| | Upper moderate disability | 10 (8.2) | 12 (9.4) | 22 (8.8) |
| | Lower good recovery | 6 (4.9) | 16 (12.5) | 22 (8.8) |
| | Upper good recovery | 8 (6.6) | 14 (10.9) | 22 (8.8) |
| Dichotomised GOSE score | Unfavourable: dead, vegetative state, lower severe disability, upper severe disability | 88 (71.0) | 78 (60.5) | 166 (65.6) |
| | Favourable: lower moderate disability, upper moderate disability, lower good recovery, upper good recovery | 36 (29.0) | 51 (39.5) | 87 (34.4) |

Tables 9 and 10 show the results of the primary analysis (hypothermia vs. standard care), primary subgroup analyses and secondary analyses of the PP population.

For binary outcomes, presentation of both absolute and relative effect sizes is recommended¹⁰³ (see Tables 6–10 for all data).

TABLE 9 The results of the primary analysis (hypothermia vs. standard care) and primary subgroup analyses in the PP population

| Analysis of primary outcome for hypothermia vs. control | Estimate (95% CI) | p-value |
|--|---------------------|---------|
| Adjusted common OR for GOSE score at 6 months ^{a,b,c} | 1.61 (0.98 to 2.61) | 0.06 |
| Adjusted OR for unfavourable outcome ^{a,b,d} | 1.62 (0.93 to 2.83) | 0.09 |
| Treatment hypothermia vs. control (unadjusted) | 1.63 (1.02 to 2.62) | 0.04 |
| Treatment hypothermia vs. control (collapsed) | 1.61 (0.98 to 2.61) | 0.06 |
| Treatment hypothermia vs. control (dichotomised) | 1.62 (0.93 to 2.83) | 0.09 |
| Subgroup analyses | | |
| Aged < 45 vs. ≥ 45 years ^d | NP | 0.03 |
| Post-resuscitation GCS motor component [score of 1 or 2 (or no extension or response) vs. 3–6 (flexion or better response)] ^d | NP | 0.79 |
| Time from injury (< 12 hours vs. ≥ 12 hours) ^d | NP | 0.02 |
| Pupillary response (both reacting vs. one reacting vs. neither reacting) ^d | NP | 0.64 |
| <p>NP, not performed.</p> <p>a An OR or common OR of < 1 corresponds to a benefit for hypothermia over control.</p> <p>b Results were adjusted for age, post-resuscitation GCS motor score, time from injury and pupillary response.</p> <p>c The eight-point GOSE was collapsed to six categories by pooling death (score of 1) with vegetative state (score of 2) and lower severe disability (score of 3).</p> <p>d The eight-point GOSE was collapsed to two categories: favourable outcome (score of 5–8) and unfavourable outcome (score of 1–4).</p> | | |

TABLE 10 Results of the secondary end-point analyses for the PP population

| Analysis of secondary outcomes: hypothermia vs. control | Estimate (95% CI) | p-value |
|---|----------------------------|---------|
| Unadjusted HR for death incidence between randomisation and 6 months | 1.62 (1.01 to 2.60) | 0.05 |
| Adjusted mean difference in squared proportion of ICP measurements of ≤ 20 mmHg on days 1–7 | 183.30 (–545.32 to 911.92) | 0.62 |
| Incidence of patients who had presence of pneumonia on days 3–7 | 1.04 (0.62 to 1.73) | 0.89 |
| Adjusted mean difference in log-transformed length of ICU stay (log-hours) ^a | 0.02 (–1.16 to 0.20) | 0.80 |
| Adjusted common OR for MOHS grade at 28 days ^{a,b} | 1.93 (0.93 to 4.00) | 0.08 |
| <p>a Results were adjusted for age, post-resuscitation GCS motor score, time from injury and pupillary response.</p> <p>b The six grades of the MOHS were collapsed to four categories by pooling dependent, fully dependent and death.</p> | | |

Ancillary analyses

Prespecified subgroups for the primary analysis were defined on the basis of the baseline covariates described (see *Table 1*), the location of the centre (UK vs. non-UK) and the volume of the centre (≥ 10 vs. < 10 participants). We performed these analyses by including an interaction term between each intervention and the relevant covariate in the ordinal logistic-regression model; a stricter level of statistical significance ($p < 0.01$) was used because of their exploratory nature.

The results of this subanalysis showed no statistically significant difference in patient outcome between UK centres and non-UK centres ($p = 0.17$) and no statistically significant difference in outcome between high-volume recruiting centres and low-volume recruiting centres ($p = 0.12$).

Modified Oxford Handicap Scale grades were analysed in the same way as GOSE scores, but we collapsed the six grades to four categories by grouping together dependent, fully dependent and death. In the analysis of the between-group difference in mortality, Cox proportional hazards regression was used to estimate the intervention effect.

Other continuous outcomes were tested with an analysis of covariance; for binary outcomes, logistic regression was used. ICP, core temperature, MAP and CPP on days 1–7 were analysed post hoc with the use of a linear model, with study days as repeated measurements with a compound symmetry covariance matrix. All of these analyses used the same covariates as were prespecified for GOSE scores, together with the baseline value of the relevant variable.

Occasionally, participants who have suffered a brain injury have severe brain swelling that does not respond to the usual treatment methods. In these cases, participants require further treatment with either drugs (barbiturates) or surgery (decompressive craniectomy).

A further covariance analysis that was carried out was the incidence of treatment escalation or stage 2 therapy failure across groups. *Table 11* shows the proportion of participants in the Eurotherm3235 Trial who developed severe brain swelling and the days on which the therapy failure occurred.

TABLE 11 Incidence of treatment escalation or stage 2 therapy failure across groups

| | Treatment group, n (%) | | |
|------------------|------------------------|-------------------------|--------------------------|
| Parameter | Hypothermia (N = 195) | Standard care (N = 192) | Overall, n (%) (N = 387) |
| First occurrence | | | |
| Day 1 | 15 (7.8) | 31 (16.4) | 46 (12.1) |
| Day 2 | 15 (7.8) | 22 (11.6) | 37 (9.7) |
| Day 3 | 14 (7.3) | 17 (9.0) | 31 (8.1) |
| Day 4 | 13 (6.8) | 14 (7.4) | 27 (7.1) |
| Day 5 | 7 (3.6) | 7 (3.7) | 14 (3.7) |
| Day 6 | 11 (5.7) | 4 (2.1) | 15 (3.9) |
| Day 7 | 9 (4.7) | 7 (3.7) | 16 (4.2) |
| Missing | 3 (1.5) | 3 (1.6) | 6 (1.6) |
| Never occurred | 108 (56.3) | 87 (46.0) | 195 (51.2) |

Harms

An AE is any untoward medical occurrence in a clinical trial subject. Many untoward events are expected in patients admitted to the ICU because of the severity of their illness and/or injury.

The treatment of any untoward medical occurrence is part of the standard care for patients admitted to the ICU. Therefore, the decision was made in the design stage of the trial that no AE data would be collected in this study.

A SAE is defined by the National Research Ethics Service in the UK¹⁰⁴ as any AE that:

- results in death
- is life-threatening
- necessitates hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect.

Death is an expected outcome in approximately 25% of all critically ill patients with severe TBI¹⁰⁵ and, therefore, it was not reported as a SAE in this study.

The specific SAE data that we collected were:

- bleeding – defined as a new haemorrhage requiring ≥ 2 units of packed red cells
- cardiovascular instability – defined as a systolic blood pressure of < 90 mmHg for ≥ 30 minutes⁸⁶ (of note, terminal hypotension data was not collected)
- thermal burns on $> 5\%$ of body surface area using the Lund–Browder chart
- cerebral perfusion pressure of < 50 mmHg for ≥ 15 minutes.

Unexpected events considered to be SAEs, that are not described above, could also be collected by investigators by using the 'other' option on the SAE form. *Table 12* shows all SAEs that were collected throughout the trial.

TABLE 12 Details of all SAEs that were collected throughout the trial

| Parameter | Category | Treatment group, <i>n</i> (%) | | Overall, <i>n</i> (%) (<i>N</i> = 387) |
|--|---|----------------------------------|------------------------------|--|
| | | Hypothermia (<i>N</i> = 195) | Control (<i>N</i> = 192) | |
| Participants who had at least one SAE ^a | All | 19 (9.7) | 10 (5.2) | 29 (7.5) |
| Number of SAEs | All | 33 | 10 | 43 |
| Number of specific SAEs | Bleeding – defined as a new haemorrhage requiring ≥ 2 units of packed red cells | 3 (9.1) | 0 | 3 (7.0) |
| | Cardiovascular instability – defined as a MAP of ≤ 90 mmHg for ≥ 30 minutes | 5 (15.2) | 2 (20.0) | 7 (16.3) |
| | CPP of < 50 mmHg for ≥ 15 minutes | 11 (33.3) | 6 (60.0) | 17 (39.5) |
| | Other | 14 (14.2) | 2 (20.0) | 16 (37.2) |
| SAE causality | Not related | 25 (75.8) | 9 (90.0) | 34 (79.1) |
| | Possibly related | 8 (24.2) | 1 (10.0) | 9 (20.9) |

^a A single patient might have multiple AEs.

Reporting of SAEs was low throughout the trial, with an overall incidence of 7.5%. Most of these events were collected in the hypothermia group. We believe that the reason for this is that the four specific SAEs that we outlined were all possible side effects of hypothermia; therefore, these SAEs may have been thought to be physiological effects of the brain injury in the standard-care group rather than being related to the trial, especially as treatment in the standard-care group was not protocolised.

Economic evaluation

Owing to the early stopping of this trial, as a result of likely futility and possible harm, it was considered by the investigators and Trial Steering Committee that an economic analysis would not make a useful contribution to the outcomes of the study; the results of the ITT analysis supported this view.

Chapter 4 Discussion

Discussion

The use of induced hypothermia in addition to standard care did not result in improved patient outcomes at 6 months after injury compared with standard care alone. Consequently, the trial was stopped early, after 387 of the intended 600 participants had been randomised, when the Trial Steering Committee and the trial sponsor agreed with the recommendations of the DSMC:

- At best, a result of futility would be expected if the trial were to continue.
- There were signs of harm with the treatment being evaluated.
- These signs included increased mortality in participants assigned to the treatment being evaluated and fewer participants assigned to the treatment being evaluated achieving 'good recovery' on the GOSE at the designated outcome assessment point of 6 months after inclusion.
- These findings were apparent when examining the study's designated primary outcome measure analysed in accordance with the study's pre-stated statistical analysis plan.

We acknowledge that the early termination of recruitment to this trial introduces the risk of bias; however, the reason for termination was accepted by the authors.

The Eurotherm3235 Trial was a large RCT that tested TH as the primary (stage 2) intervention to reduce ICP after TBI. Literature at the time of protocol development indicated that at least one episode of ICP of > 20 mmHg occurred in 50% of participants with TBI who received mechanical ventilation and ICP monitoring.¹⁰ In contrast to this, participant screening data collected during this trial indicated that fewer participants than expected (only 16% of screened participants) developed raised ICP of > 20 mmHg.

Standard care followed the best practice recommended in the Brain Trauma Foundation guidelines⁸⁶ but was not prescribed in the protocol. Guidelines for induction and maintenance of hypothermia and for control of shivering were developed and discussed with centres during their site initiation meeting. It should be noted that the hypothermia guideline only prescribed the technique for the induction of hypothermia rather than the maintenance; centres were able to use whichever cooling technique they would normally use for maintenance of hypothermia. If a participant was randomised to the hypothermia group, copies of these guidelines were given to the relevant centre to use.

We found no significant between-group difference regarding to the time from injury to initiation of hypothermia (< 12 or ≥ 12 hours). This differs from a previous review, which found that outcome was improved when hypothermia was initiated within 12 hours of injury.³⁶ However, there were not enough participants randomised within 12 hours after injury in this trial to be confident of having excluded a subgroup effect for the time from injury. Those trials in which hypothermia for neuroprotection was induced very soon after injury and which were judged to be of higher quality and to have a lower risk of bias¹³ also showed trends towards unfavourable outcomes^{15,16} or were stopped for futility.^{17,18}

In this trial, barbiturate infusion was reserved for participants who had uncontrolled raised ICP despite treatment with all stage 1 and 2 treatments. We found that barbiturate infusion to reduce ICP was used more frequently, and earlier, in the control group than in the hypothermia group. It is plausible that barbiturate infusion may have somehow been beneficial to participants in the control group, but this hypothesis is not within the remit of this trial and requires further testing. There was no statistical difference in the use of decompressive craniectomy between the two groups.

The trial was designed to be pragmatic and to focus on functional outcome rather than on detailed mechanistic pathways throughout the participants' ICU stays. In usual practice, the intensity of a stage 2 therapy is adjusted in the ICU setting depending on its effect on haemodynamic variables: ICP, MAP and CPP. As there were no, or limited, data on the benefits and harms of standard stage 2 interventions at the time of writing the protocol, we decided not to record which and/or how many stage 2 therapies were delivered to participants. Our findings show that there were no clinically important differences in these variables between the two groups.

We accept that the result, which suggests the possible harm of hypothermia, could be attributable to a biological effect of hypothermia or to the harms or benefits of the other therapies used differentially in the two groups. This trial did not assess the biological effects of other treatments administered during hypothermia; therefore, no conclusion regarding this hypothesis could be made. Furthermore, the main entry criterion for this trial was raised ICP of ≥ 20 mmHg, which is the definition of raised ICP given in the Brain Trauma Foundation guidelines.⁸⁶ Consequently, the benefits and risks of hypothermia, when used to treat severe intracranial hypertension that is not responsive to any stage 2 treatments applied before initiation of hypothermia, were not assessed as part of this trial.

This trial found that ICP was well controlled in both groups (see *Figure 6*). Detailed results show, however, that ICP was more difficult to control in the standard-care group, with more stage 2 therapy failures observed in this group. This suggests that TH was effective in reducing ICP; however, it did not improve functional recovery more than treatment with standard care alone. The benefits and harms of any other interventions that successfully reduce ICP have not been assessed as part of this trial. We now believe that more adequately powered clinical trials of common therapies used to reduce ICP, such as hypertonic therapy, barbiturates and hyperventilation, are required to assess their potential benefits and risks to patients.

Limitations

A limitation of this study was the inability to blind the hypothermia intervention. This is problematic for any trial of TH and is primarily because of the equipment required and the obvious physiological differences between groups including, but not limited to, participants' core temperature. Cooling to normothermia was, however, permitted in the standard-care group; therefore, it is possible that some relatives were masked from the intervention/allocated group. We believe that this limitation was overcome, however, by blinding the follow-up and GOSE scoring.

A further limitation in the design of the trial is that we allowed SAEs to be collected in both groups when the four specific SAEs that we outlined (see *Chapter 3, Harms*) were all possible side effects of induced hypothermia. This resulted in more frequent SAE reporting in the hypothermia group and introduced reporting bias. The same clinical events may have been seen in the control group but may have been considered expected consequences of admission to intensive care following severe brain injury, and may not have been reported as SAEs linked to being in the trial.

Generalisability

The Trial Steering Committee and trial sponsor accepted the recommendation of the DSMC after its ninth meeting in full and terminated recruitment early. Early stopping of any trial can potentially reduce the external validity of the results; however, the burden of proof required for early stopping for possible harm is considerably lower than that for overwhelming evidence of efficacy.¹⁰⁶ In this case, the GOSE scores collected after the decision to terminate confirmed the result of the trial detailed earlier.

Although the trial was open, we believe that the external validity was strong, as centres:

1. were able to use their own technique for maintenance of hypothermia
2. could rewarm the participant based on their physiological parameters and condition from day 3 onwards
3. could cool participants to normothermia in the control group for fever control
4. could escalate care to stage 3 interventions if/as soon as was required in both groups.

The prescribed induction of hypothermia means that the same technique was used to initiate hypothermia in all participants. We know that compliance with the guideline was good, as *Figure 7* shows the rapid reduction in temperature to 35 °C, and treatment compliance showed that 97.1% of core temperature observations were within range in the hypothermia group. This strengthens the internal validity of the trial and its result. The use of a blinded outcome assessor also improved the internal validity of the trial as the same method for scoring was used for all GOSE questionnaires and scoring was carried out by the same researcher throughout the trial. Furthermore, the imputed algorithm in the trial online database was used to ensure that there was no human error/bias in scoring.

The trial involved 387 participants from 47 centres across 18 countries worldwide, and all were able to use their own maintenance technique for hypothermia without a protocolised control group. We therefore believe that the results can be generalised to any global setting. The cooling intervention studied was already being used in clinical practice in each of these centres and was tested in the way that centres normally used it.

Chapter 5 Updated systematic review of therapeutic hypothermia for adult patients following traumatic brain injury

The protocol and Cochrane domain-based assessment of bias for this systematic review can be found in *Report Supplementary Material 1* and *2*.

Evidence before this study

Therapeutic hypothermia is commonly used in the treatment of adult TBI. There has been debate over the efficacy of TH following the publication of two multicentre RCTs^{107,108} that showed either harm or no clinical benefit from the use of TH.

The following databases were searched from 1 January 2011 to 31 March 2016: CENTRAL (Cochrane Central Register of Controlled Trials), MEDLINE, PubMed and EMBASE. Only foreign articles published in the English language were included. Only articles that were RCTs investigating adult TBI sustained following an acute, closed head injury were included. Quality was assessed using the Cochrane Collaboration's tool¹⁰⁹ for assessing the risk of bias and a modified Jadad score.

Added value of this study

This study adds key knowledge to the evidence base that may go some way to explain discrepancies in results between the most recent published RCTs and reviews. When high-quality studies are analysed together, they do not support the role of TH as a treatment for adult TBI with respect to resultant mortality, outcomes and incidences of pneumonia. Crucially, this review is able to highlight the importance of the control group, as fever in the control group led to significantly more poor outcomes; therefore, potentially overemphasising the benefit of TH.

Implications of all the available evidence

Overall, this systematic review of RCTs does not support the role of TH in adult TBI patients, which is in keeping with the conclusions of the two most recent RCTs.^{1,107}

Introduction

There has been debate over both the overall efficacy of TH and the degree of hypothermia required to gain any positive clinical effect in the treatment of adult TBI. A previous study found some clinical benefit to TH in TBI,¹¹⁰ however the Eurotherm3235 Trial¹ was stopped early concerns over participant safety.^{1,110} Additionally, a RCT published in 2016¹¹¹ showed that strict fever control resulted in similar clinical outcomes as prolonged TH. The most recent systematic reviews^{1,112} have also reported conflicting results.¹¹⁰ A 2016 meta-analysis¹¹¹ was unable to demonstrate improved survival and suggested that TH may increase the risk of new pneumonia and cardiovascular complications. Conversely, a large meta-analysis reported a benefit of TH but it was discussed that this benefit may be attributable to the fact that a large number of observational studies were included in this analysis.¹¹³ Despite this discourse, TH is still routinely used in the treatment of raised ICP in the context of adult TBI.

Aims

The primary aim of this systematic review was to use RCTs to update the evidence base on the use of TH when administered to adult patients in intensive care following TBI. The main outcomes of interest were mortality, poor (unfavourable) outcomes and new pneumonia.

Secondary aims were (1) comparison of control group, (2) early (< 24 hours from injury) compared with late (> 24 hours from injury) TH, (3) the effect of duration of follow-up on mortality outcomes and (4) whether or not the date of publication had any effect on the outcomes of TH trials.

Materials and methods

Search methods for identification of trials

Searches were not restricted by date or by publication status. The search strategy is recorded in the protocol (see *Report Supplementary Material 1*). The dates were chosen to be complementary to, and have an overlap of 12 months with, the previous systematic review¹¹⁰ conducted by one of the co-authors; this was to capture any trials that were in the process of publication.

Other sources

Reference lists of all included trials and relevant review articles were hand-searched by the authors. When appropriate, authors were contacted directly for further information.

Ethics approval and consent

This study did not require ethics approval or individual participant consent.

Methodological criteria for selection of randomised controlled trials

The inclusion criteria were that trials must (1) be RCTs, (2) investigate adult moderate (i.e. a GCS of 9–12) or severe (i.e. a GCS of ≤ 8) TBI and (3) investigate TBI that was sustained following an acute, closed head injury. The use of TH was the intervention of interest. RCTs that did not have two treatment arms with TH compared with a control group were excluded. For the purpose of this review TH is defined as any intervention with the intention of reducing core body temperature to below the physiological norm (36 °C). The method of temperature reduction was noted during data extraction. Participant outcomes at follow-up were assessed using mortality and poor outcome data. There was a particular emphasis on outcomes recorded on a scale, for example the GOS, the Ranchos Los Amigos Scale or an equivalent scale. Reporting of poor outcomes includes mortality figures, in accordance with the usual reporting methodology.

Participants/population

To be included in the review, participants must be adults and must have sustained an acute, closed head injury. Adults were defined as being at the legal age for consent in the country the study was conducted in. Articles were excluded if they contained only neonatal or paediatric participants or participants with open head injuries (including gunshot wounds).

Only trials that met all inclusion criteria, and that did not meet any of the exclusion criteria, were included.

Data extraction

The output of all searches was exported into Microsoft Word (Microsoft Corporation, Redmond, WA, USA) and two co-authors were involved at each stage of review. The PRISMA statement¹¹⁴ was followed at all three stages of review. First, duplicates from across the databases were removed. Following duplicate removal, the abstracts and titles were assessed against our inclusion and exclusion criteria. Second, abstracts were read in detail against the defined criteria. Third, the remaining articles were read in full and the final decision on inclusion or exclusion was made. A third reviewer was available to resolve any discrepancies in agreement. See *Figure 9* for the PRISMA flow diagram.

Bias

The Cochrane Collaboration's tool for assessing the risk of bias¹⁰⁹ was used during the data extraction process. The following areas were assessed: selection, performance, detection, attrition and reporting bias. This covered the relevant areas of allocation concealment, blinding, ITT analysis and completeness of follow-up. In comparison to the previous review,¹¹⁰ academic bias was also included at this stage; academic bias was considered to be present if two or more RCTs included in this systematic review were by the same author.

The included RCTs were put into a domain-based assessment of risk of bias (see *Report Supplementary Material 2*), which included potential confounding factors. The maximum score available was 18 points, with a high score equating to the least risk of bias. Those scoring 14–18 (top quartile) had a low risk of bias and those scoring < 14 had a high risk of bias, as assessed by the domains.

Quality

A modified Jadad score was used to assess the quality of the included RCTs.¹⁴ Blinding was not possible because of the nature of the intervention. Regarding randomisation, 1 point was awarded for randomisation being mentioned and a further point was awarded if randomisation was appropriate. No points were awarded if randomisation was not stated. Then, 1 point was given if all participants entered into the trial were accounted for at the end of the trial. This gave a maximum modified quality score of 3 points per RCT. Studies scoring 0, 1 or 2 points were considered low quality, with those scoring 3 points considered high quality. The quality of included RCTs was also assessed using the Cochrane Collaboration's tool for assessing the risk of bias.¹⁰⁹

Data synthesis

Review Manager (RevMan; version 5.3; Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) was used for data analysis.

Statistical analyses

Mortality, poor outcomes (including mortality) and pneumonia data were extracted and the RR and corresponding 95% CIs were calculated. The Mantel–Haenszel approach was used to assess the significance of the overall RR (RR_{overall}) as an effect estimate using the null hypothesis $RR_{\text{overall}} = 1$ using the z-test.

As per the Cochrane Handbook,¹⁰⁹ both fixed and random effects were generated in the first instance for each analysis.

Statistical heterogeneity was assessed using the chi-squared and *I*²-index tests to estimate the degree of trial variability. Thresholds for interpretation of heterogeneity were also taken from the Cochrane Handbook, with 0–40% representing possible low heterogeneity, 30–60% representing possible moderate heterogeneity, 50–90% representing possible substantial heterogeneity and 75–100% representing possible high heterogeneity.

Sensitivity analysis

Forest plot analyses were performed for all studies and were performed separately for those deemed at least risk of bias as assessed using a Cochrane-based evaluation.

Results

The final analyses included 21 trials,^{1,48,59,60,63,64,69,71,73–77,107,108,115–120} including data for two new trials.^{1,107} *Figure 8* shows the PRISMA flow diagram for inclusion. One trial included in the 2014 review has now been published with additional data.¹⁰⁷ These trials enrolled 2299 participants. Only one trial did not include mortality data.^{48,107} The quality of included RCTs and the characteristics and data extraction of the included studies is shown in *Appendix 5*. The primary and secondary aims are addressed below. All subgroup analyses had fixed- and

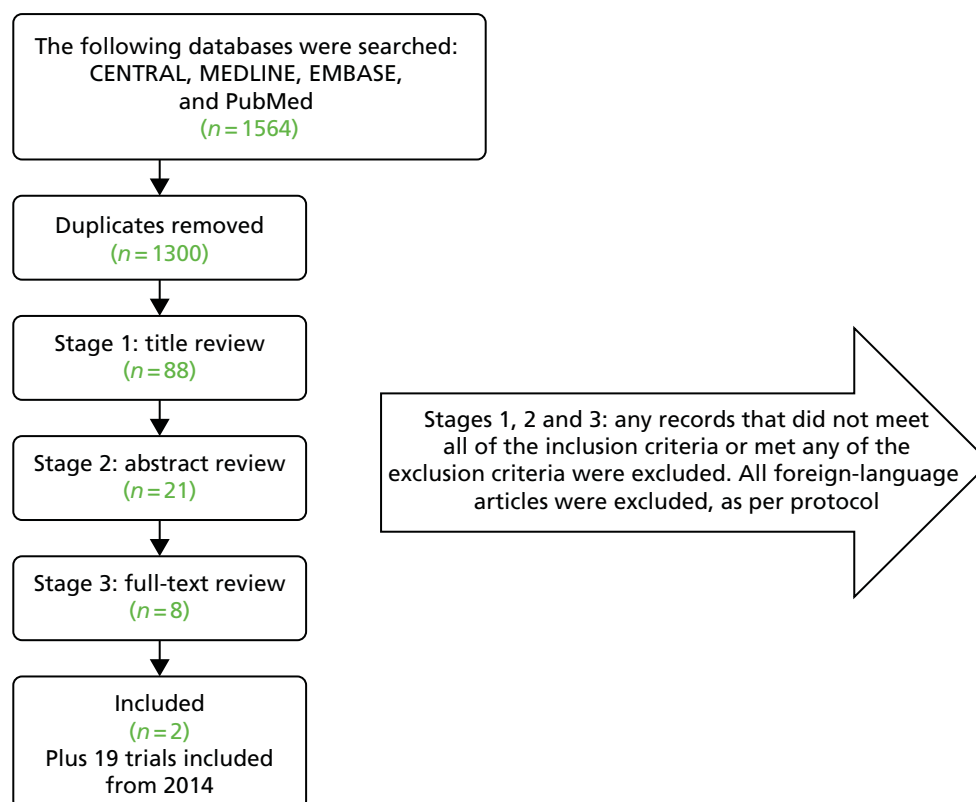


FIGURE 8 The PRISMA flow diagram.

random-effects models generated. There was no difference in statistical significance so fixed-effects models have been used throughout. When RCTs had ‘not estimable’ in the RevMan plots, they were removed from the graph as they did not contribute statistically. *Appendix 6* details the RCT inclusion differences between this systematic review and previous large reviews.

Risk of bias of included randomised controlled trials

There were two methods used for assessing the quality of included RCTs: the Cochrane Collaboration’s tool for assessing the risk of bias and a modified Jadad score.¹⁰⁹

Using the Cochrane Collaboration’s tool for assessing the risk of bias, each RCT was given a score out of 18. Two RCTs scored ≥ 14 (top quartile) so were considered as having a low risk of bias. Conversely, 18 RCTs scored ≤ 13 and so were considered as having a high risk of bias. See *Appendix 7* on assessment of bias. These scores were used for further analysis of risk of bias for the primary outcomes of mortality, poor outcomes and new pneumonia.

Quality of included randomised controlled trials

On the modified Jadad score, those scoring 3 were high quality and those scoring 0, 1 or 2 were low quality. In total, six of the included studies were classed as high quality and 14 studies were classed as low quality. These scores were used for further analysis of quality for the primary outcomes of mortality, poor outcomes and new pneumonia.

Primary aims

Mortality results

Mortality was reported in 20 studies. *Figure 9* shows mortality data for 20 studies, totalling 2270 participants. When the results of these 20 RCTs were statistically aggregated, there was a significant reduction in mortality in the TH group (RR 0.84, 95% CI 0.74 to 0.96; $p = 0.01$). A fixed-effects model was used and supported by a moderate I^2 -index ($I^2 = 43\%$).

Mortality results with quality and risk-of-bias analysis

Six of the included studies were classed as high quality and 14 studies were classed as low quality, as per the modified Jadad score assessment of risk of bias (*Figure 10*). The high-quality studies showed a higher mortality in the TH group (RR 1.22, 95% CI 0.99 to 1.57), but this result was not significant ($p = 0.06$). The low-quality studies showed a higher mortality in the control group (RR 0.69, 95% CI 0.58 to 0.81; $p < 0.00001$). There was significant heterogeneity between the two subgroups ($I^2 = 94.2\%$).

Risk-of-bias assessment was also undertaken using the Cochrane Collaboration's tool and again affected mortality outcomes (*Figure 11*). Two studies had a low risk of bias and showed a higher mortality in the TH group (RR 1.37, 95% CI 1.04 to 1.79; $p = 0.02$), whereas the 18 studies having a high risk of bias showed a higher mortality in the control group (RR 0.72, 95% CI 0.62 to 0.84; $p < 0.0001$).

Poor outcomes

Twenty-one trials reported on poor outcome involving 2286 participants. There were significantly more poor outcomes in the control group than in the TH group (RR 0.81, 95% CI 0.75 to 0.87; $p \leq 0.00001$) (*Figure 12*), with possible substantial heterogeneity ($I^2 = 72\%$).

Poor outcome results with quality and risk-of-bias analysis

There were six high-quality studies that showed no significant difference in poor outcomes between the control and TH groups (RR 1.03, 95% CI 0.92 to 1.16; $p = 0.56$). However, when the 15 low-quality studies were analysed together, they showed more poor outcomes in the control group (RR 0.69, 95% CI 0.62 to 0.76; $p < 0.00001$).

When the two low-risk-of-bias studies were analysed, they showed that poor outcomes were more likely in the TH group (RR 1.16, 95% CI 1.02 to 1.32; $p = 0.03$). Conversely, when the 19 studies with a high risk of bias were analysed together, they showed significantly more poor outcomes in the control than the TH group (RR 0.70, 95% CI 0.64 to 0.77; $p < 0.00001$).

New pneumonia results

Thirteen studies reported new pneumonia, accounting for 1128 participants. There was significantly more new pneumonia in the TH group (RR 1.43, 95% CI 1.15 to 1.78; $p = 0.001$) (*Figure 13*) when all studies were analysed together.

New pneumonia results with quality and risk-of-bias analysis

There were three high-quality studies that, when analysed together, showed no significance in new pneumonia between the two groups (RR 1.33, 95% CI 0.79 to 2.25; $p = 0.28$). In contrast, the 10 low-quality studies suggested significantly more new pneumonia in the TH group (RR 1.35, 95% CI 1.07 to 1.69; $p = 0.01$).

The two low-risk-of-bias studies showed no significant difference in new pneumonia between the two groups (RR 1.41, 95% CI 0.72 to 1.84; $p = 0.32$), whereas the 11 studies having a high risk of bias suggested significantly more new pneumonia in the TH group (RR 1.47, 95% CI 1.17 to 1.84; $p = 0.0008$).

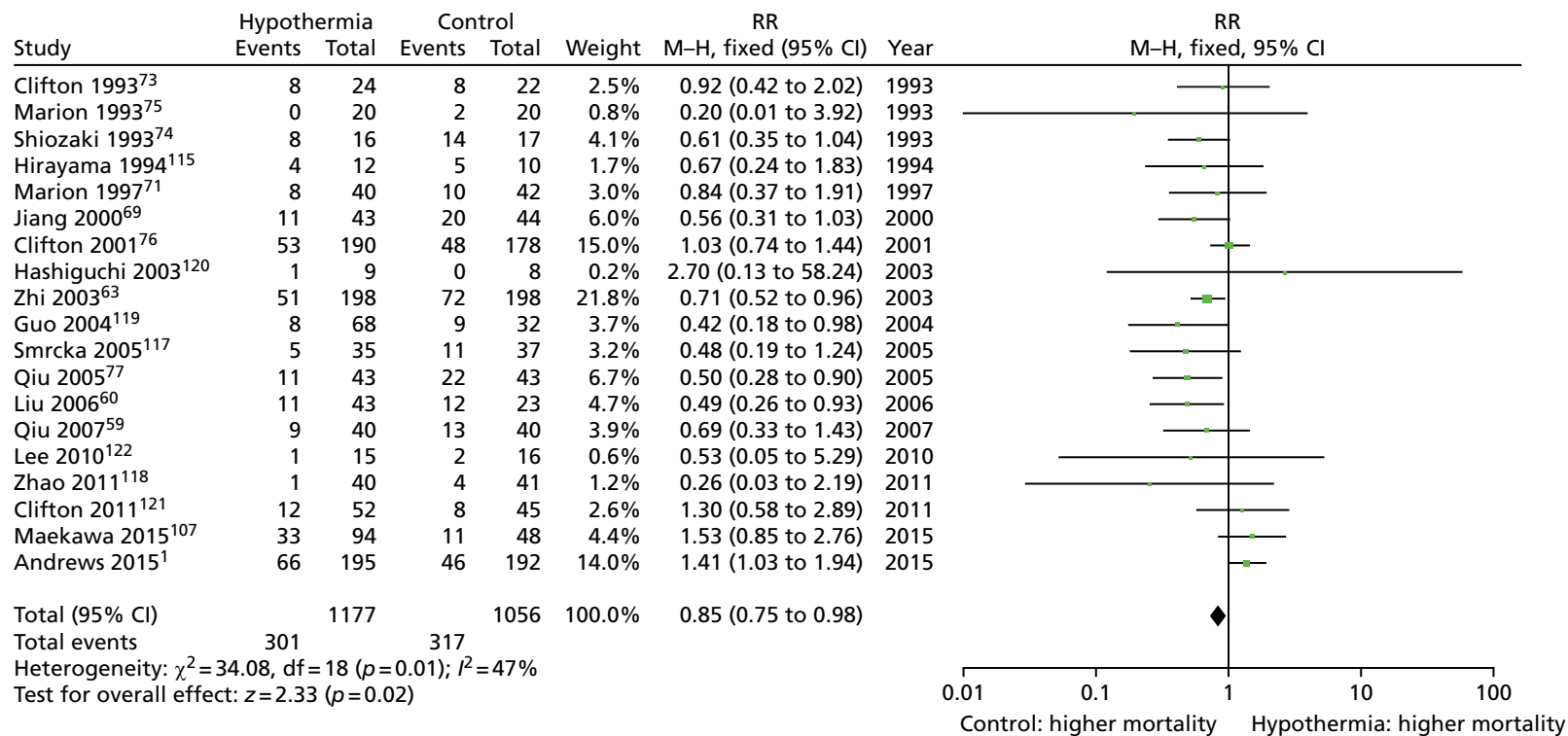


FIGURE 9 Forest plot of mortality data for 20 studies. M-H, Mantel-Haenszel.

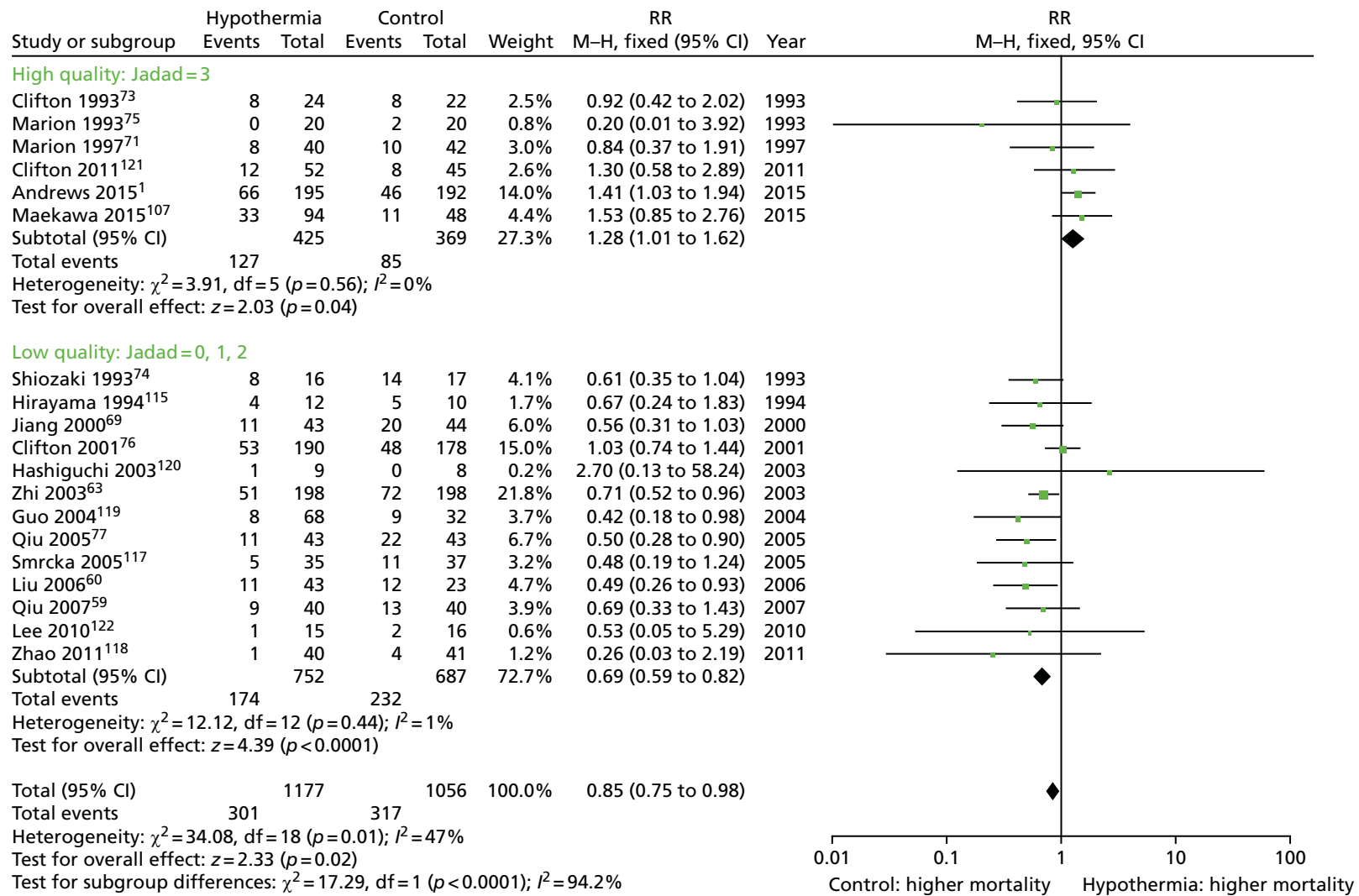


FIGURE 10 Mortality results with quality and modified Jadad score assessment of risk-of-bias analysis. M-H, Mantel-Haenszel.

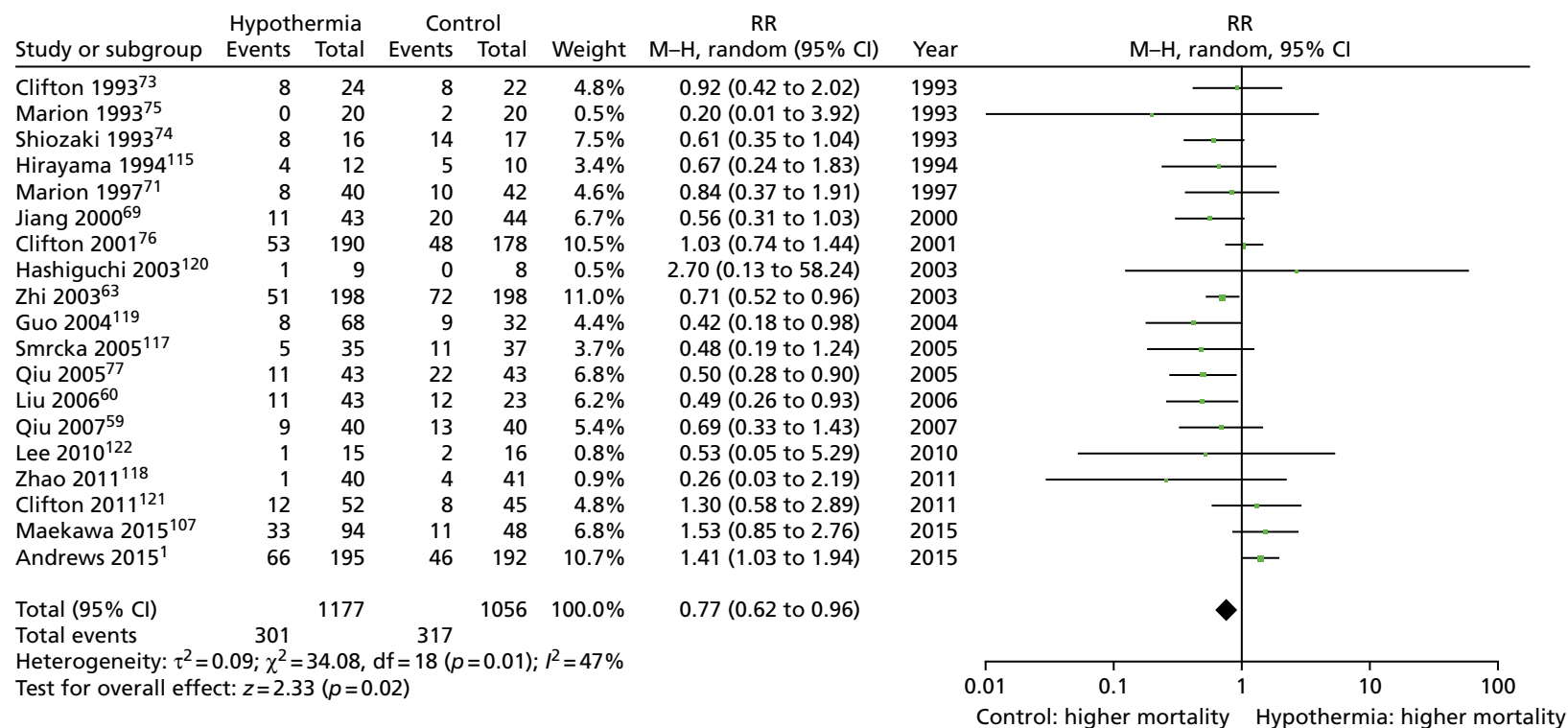


FIGURE 11 Forest plot of mortality results with quality and Cochrane Collaboration assessment of risk-of-bias analysis. M-H, Mantel-Haenszel.

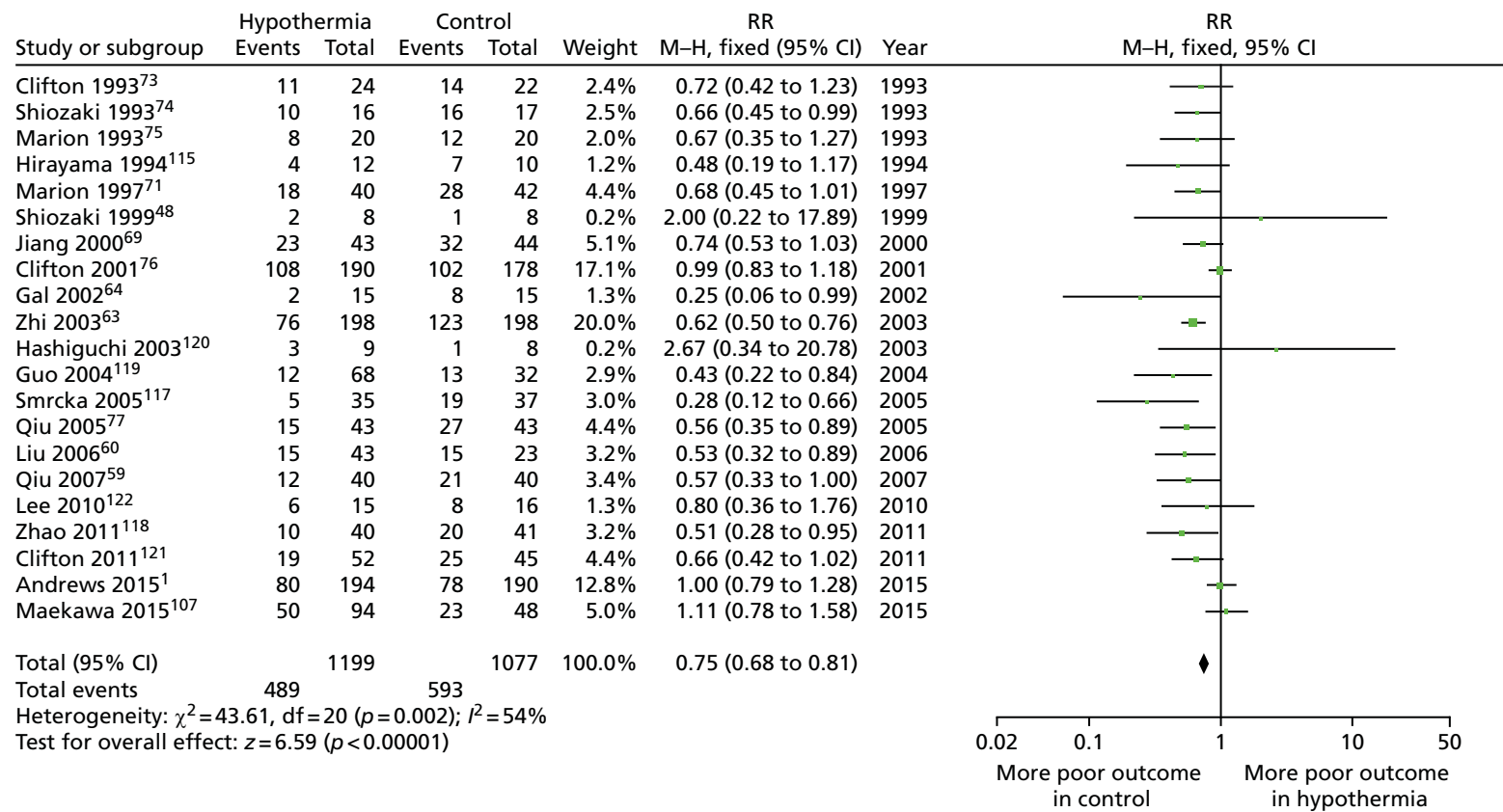


FIGURE 12 Forest plot of poor outcome. M-H, Mantel-Haenszel.

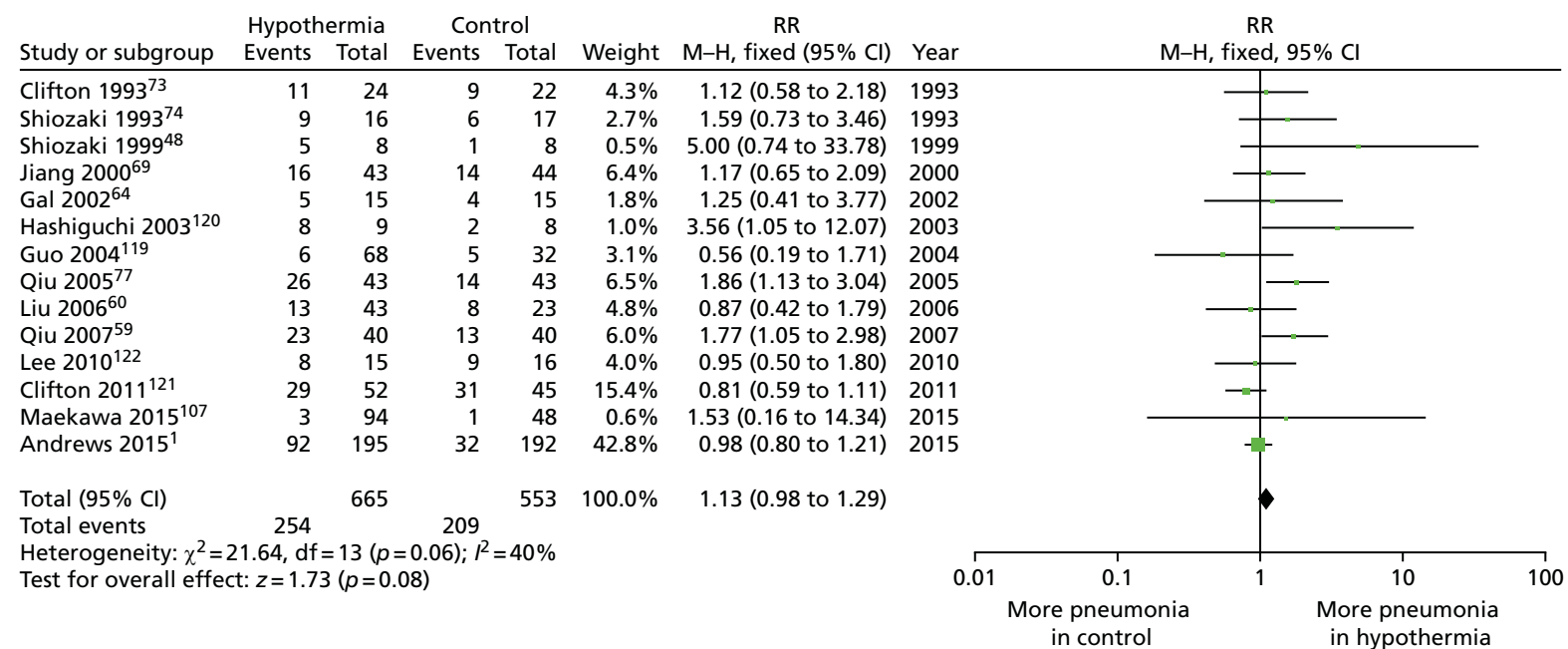


FIGURE 13 Forest plot of new pneumonia data. M-H, Mantel-Haenszel.

Secondary aims

Mortality: comparison of control groups and comparison of controlled normothermia temperature ranges

The first subanalysis on mortality specifically assessed the methodology used for temperature management in the control groups. There was no significant difference in mortality between the TH group and the control group with controlled normothermia (RR 0.89, 95% CI 0.74 to 1.08; $p = 0.25$) with possible low heterogeneity ($I^2 = 25\%$). However, there was significantly greater mortality in the no temperature control group than in the TH group (RR 0.81, 95% CI 0.68 to 0.97; $p = 0.02$) with possible substantial heterogeneity ($I^2 = 63\%$).

The results for those RCTs that implemented controlled normothermia of any degree were analysed in isolation. The groups were split into those that ensured that their control groups were $< 38^\circ\text{C}$ and those that included 38°C within their normothermia control range. Those studies that stated controlled normothermia without specific temperature ranges were placed in the latter group. Those studies that controlled to $< 38^\circ\text{C}$ showed no significant difference in mortality outcomes between the control group and TH group (RR 1.01, 95% CI 0.82 to 1.32; $p = 0.73$). Contrastingly, those control groups that included 38°C within their normothermia range showed significantly more mortality in their control groups (RR 0.61, 95% CI 0.44 to 0.87; $p = 0.005$).

Early therapeutic hypothermia compared with late therapeutic hypothermia

When mortality was analysed accounting for timing of TH from time of TBI, there were significant differences between the subgroups (Figure 14). For those participants with early hypothermia (< 24 hours from injury), there was significantly greater mortality in the control group than in the TH group [RR 0.76, 95% CI 0.64 to 0.90; $p = 0.001$ (1542 participants)] with possible low heterogeneity ($I^2 = 2\%$). Whereas, among those participants with TH induced ≥ 24 hours after injury, there was no significant difference in mortality between the control and TH groups [RR 1.08, 95% CI 0.86 to 1.34; $p = 0.51$ (641 participants)] with possible substantial heterogeneity ($I^2 = 79\%$). There was also possible substantial heterogeneity ($I^2 = 83.5\%$) between the early and late hypothermia subgroups.

Mortality: effect of duration of follow-up

There was variation between the RCTs regarding duration of follow-up. Two groups were created that analysed those RCTs with follow-up for 3 months (five studies; 271 participants) compared with those with follow-up for > 6 months (14 studies; 1999 participants) (Figure 15). For those followed up for 3 months, there was no significant difference in mortality between the control and TH groups (RR 0.73, 95% CI 0.47 to 1.17; $p = 0.20$) with possible low heterogeneity ($I^2 = 0\%$), whereas studies with follow-up for > 6 months showed significantly greater mortality in the control group (RR 0.85, 95% CI 0.74 to 0.98; $p = 0.02$), there was possible moderate heterogeneity in this subgroup ($I^2 = 55\%$). There was no heterogeneity between the two subgroups ($I^2 = 0\%$).

Mortality: date of publication

Those studies that reported mortality data were split into two groups: five were published before 2000 (223 participants) and 15 were published in or after 2000 (2047 participants). Those published before 2000 showed no significant difference in mortality between the groups (RR 0.71, 95% CI 0.49 to 1.04; $p = 0.08$), whereas those studies published in or after 2000 found higher mortality in the control group than the TH group (RR 0.86, 95% CI 0.74 to 0.99; $p = 0.03$) (Figure 16).

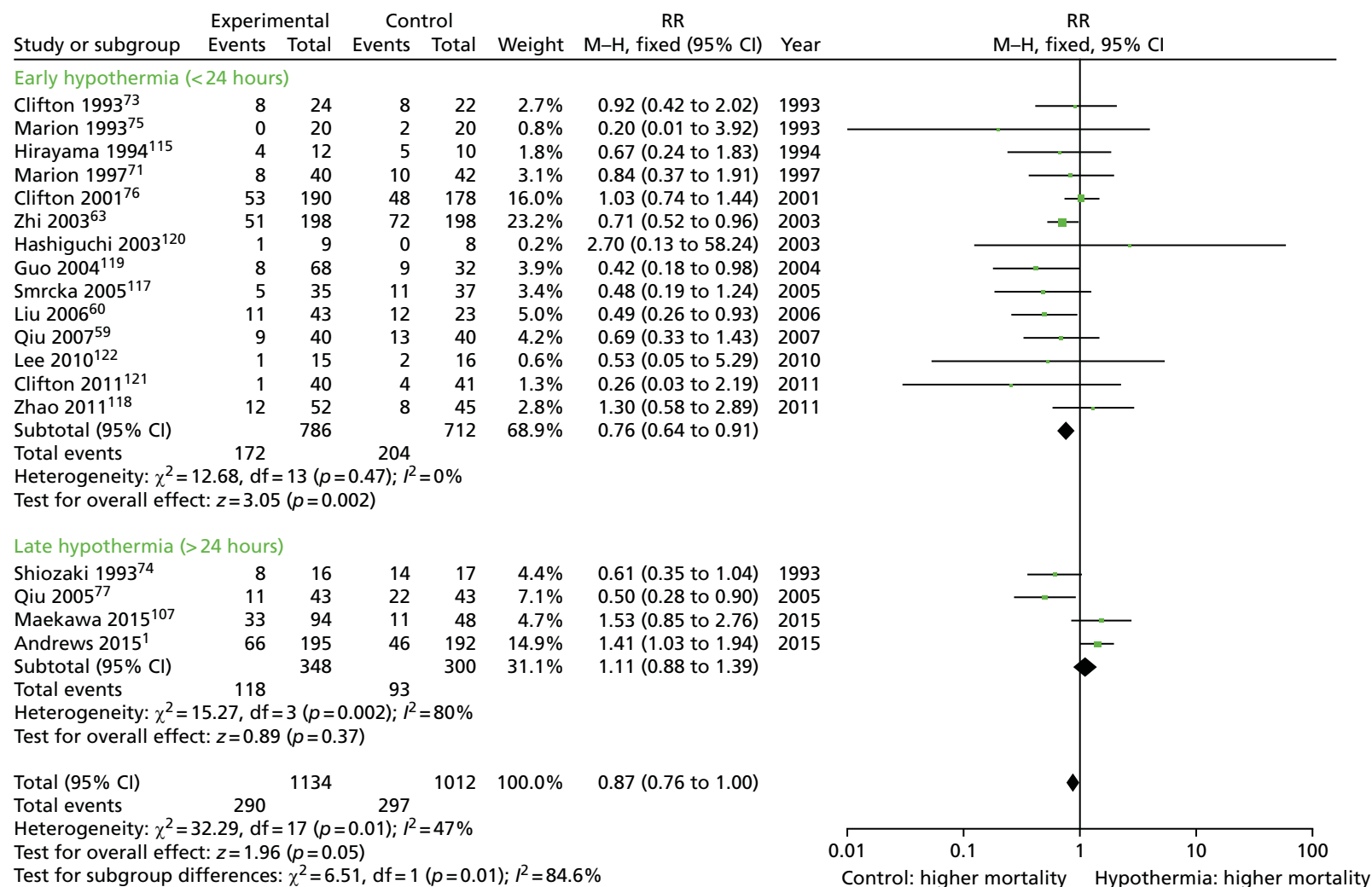


FIGURE 14 Forest plot of mortality analysed accounting for timing of TH from time of TBI. M-H, Mantel-Haenszel.

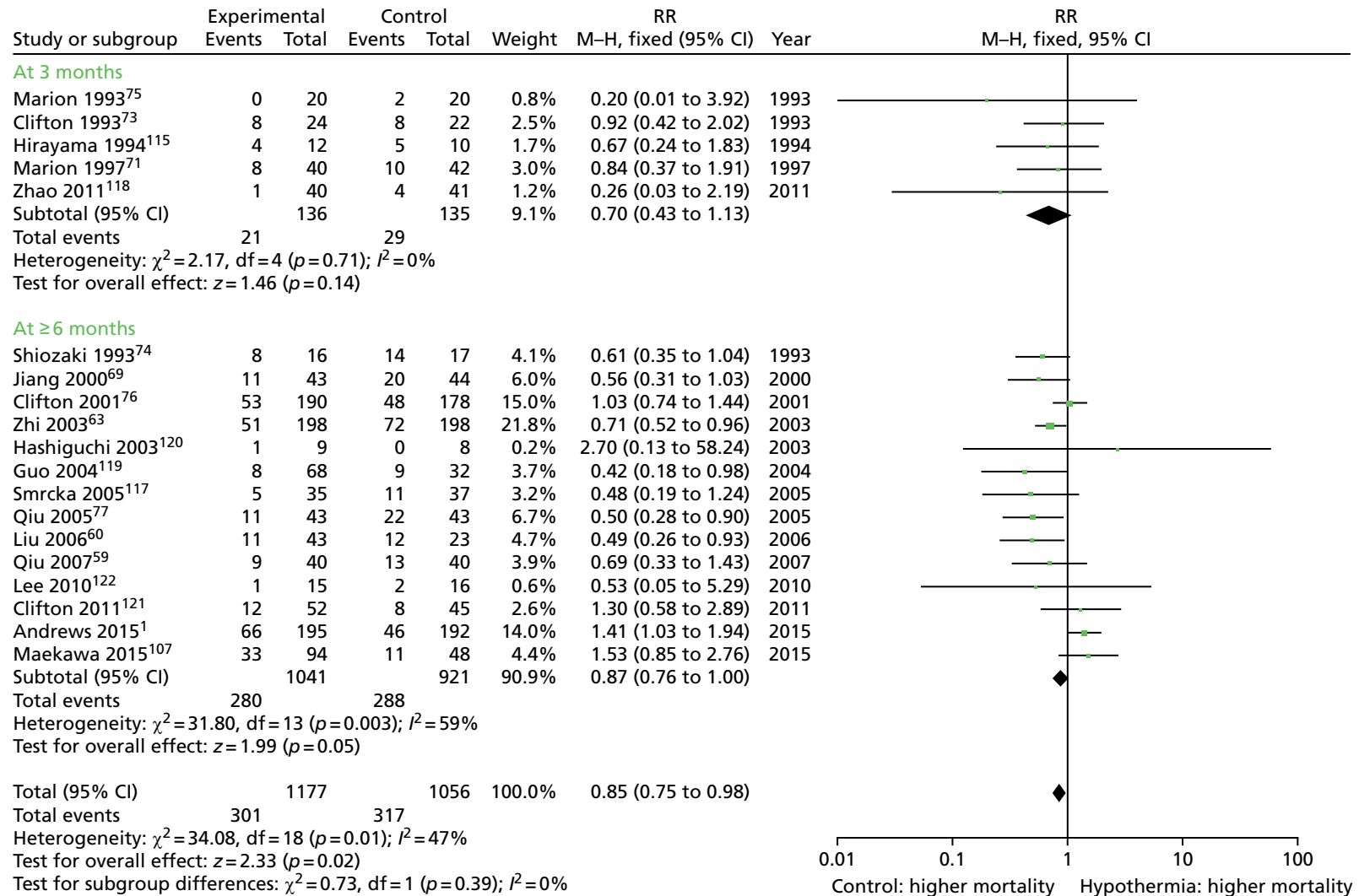


FIGURE 15 Forest plot of the effect of duration of follow-up on trial results. M-H, Mantel-Haenszel.

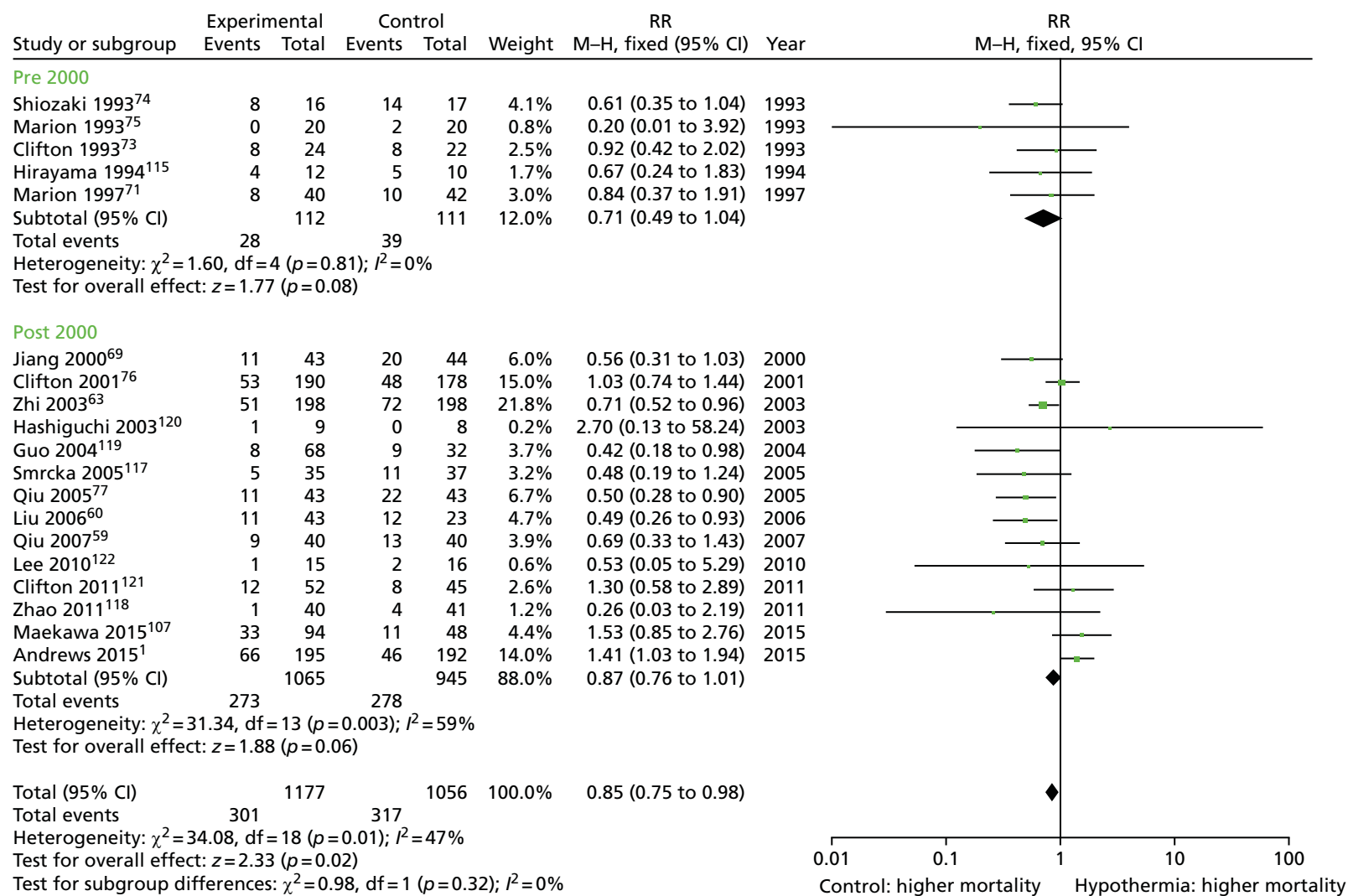


FIGURE 16 Forest plot of the effect of date of publication on outcome. M-H, Mantel-Haenszel.

Discussion

Summary of results

Overall, the results of this systematic review shed doubt on the overall outcome benefits of TH. Low-quality studies are more likely than high-quality studies to show that TH improves mortality. In addition, this review also highlights the importance of temperature management in the control group of TH trials and, in particular, the avoidance of fever.

Explanation of results

Adding to the literature, this review has shown that the control group management is important in assessing the efficacy of TH. When the temperature of the control group is controlled (controlled normothermia), avoiding fever, then TH was no longer beneficial. Furthermore, when controlled normothermia included 'fever' temperatures then the control group had a greater mortality. This is significant because it suggests that it is not just the implementation of TH that is important, but also the maintenance of adequate fever control. The importance of fever control has implications for the conclusions suggested by RCTs; for example, the Eurotherm3235 Trial had a control population with values of normothermia and the results showed harm from TH. Studies that do not adequately maintain normothermia in their control groups may be overestimating the benefits of TH, as worse overall outcomes in the control groups may be down to poor fever control rather than lack of TH.

Subgroup heterogeneity appears to be important in a variety of analyses. When looking at the induction of TH, there is a lower mortality in those who had TH implemented within 24 hours; however, cooling after 24 hours conferred no mortality benefit compared with the control treatment. This could suggest that cooling early is most beneficial or that there are differences between the subgroups; this is supported by the possible substantial heterogeneity. The results of the ongoing POLAR (Prophylactic Hypothermia trial to Lessen Traumatic Brain Injury) study¹²³ of early hypothermia for neuroprotection could provide further evidence to support this hypothesis. Those patients with late TH may have more severe injuries with more difficult to control ICP meaning that treatment was less likely to be successful regardless of time of TH onset. The two most recent RCTs both investigated late-onset TH.^{1,107}

Other studies have shown that subgroup differences are important in relation to surgical intervention; this is not always accounted for during statistical analysis of mortality and poor outcomes. These studies have provided evidence that TH may be more beneficial in those patients who are cooled after surgical haematoma evacuation than in those with diffuse brain injury. This review was unable to investigate this further because diffuse and focal TBI patients were commonly grouped together during data analysis.

Overall, this finding is important as it suggests that there may be certain subgroups of TBI patients who are more likely to benefit from TH. Differences could depend on the type of injury, surgical intervention before TH, early or late cooling and the temperature management within the control group. With all of these possible confounding factors, it is unsurprising that there are conclusion discrepancies among the most recent reviews.

Quality of evidence

Two methods were used to assess quality and the risk of bias: a modified Jadad score was used in conjunction with a domain-based assessment for risk of bias. The two latest RCTs^{1,107} were of high quality and had a low risk of bias. However, all other studies showed a high risk of bias as assessed by the objective domains. Previously, concern has been expressed that small, single-centre studies are distorting the conclusions.¹¹⁰ This review highlights the importance of this as, when the larger, higher-quality RCTs were analysed separately, they showed consistently different conclusions to other trials.

Deviation from systematic review protocol

The original primary and secondary outcomes remained as published in the protocol (see *Report Supplementary Material 1*). However, several additional subgroup analyses were added as secondary outcomes following protocol publication.

Of the original secondary aims, some subgroup analyses could not take place because of a lack of information supplied within RCTs or homogeneity between the studies. These were depth of cooling on outcomes, effect of rate of rewarming, the duration of cooling on outcomes and the use of propofol sedation.

Data extraction was completed as per protocol. There was always agreement between the two co-authors undertaking the data extraction but a reason for exclusion of an article was not always documented.

The Cochrane Collaboration's tool for assessing the risk of bias¹⁰⁹ was used rather than the 1998 Downs and Black checklist.¹²⁴ The modified Jadad score for trial quality was added to increase the objectivity for claims of quality and risk of bias.

Limitations of the review

The main limitations of the previous reviews were the inclusion of many single-centre, low-quality RCTs; this has now been partly addressed with the addition of the two latest RCTs. However, as discussed above, underlying subgroup differences may be affecting the overall conclusions.

There was significant variation in the length of follow-up post injury, ranging from 3 months to 2 years. This has also been a factor in other systematic reviews. It is not possible to control this confounder because of the variations in the standalone RCT protocols. In the context of hypothermia after cardiac arrest, it has been suggested that 6 months is the earliest time point that neurological status should be assessed.¹²⁵

This review updated some of the original data used in the Crossley *et al.*¹¹⁰ paper and these data extraction amendments have been included and analysed in this paper.

Similarities to, and differences from, other reviews

Although this review has several similarities to recent review papers, it also has some significant differences. Crossley *et al.*¹¹⁰ were able to demonstrate a significant reduction in mortality and poor outcomes with the use of TH. However, Zhu *et al.*¹¹¹ found no difference in either of these outcomes between the TH and control groups. The latter systematic review is in agreement with other RCTs published since 2015: the Eurotherm3235 Trial found evidence of harm from TH,¹ whereas B-HYPO (Brain Hypothermia study)¹⁰⁷ found no improvement in outcomes from TH when compared with strict fever control or controlled normothermia; both studies assessed the use of late TH post TBI. Importantly, both of these RCTs avoided fever in their control groups, which does differ from the control groups of previous RCTs.^{110,111} Previous systematic reviews reported a general belief that TH was associated with new pneumonia. However, until this review, only Zhu *et al.*¹¹¹ had been able to show significance from this result. This current systematic review has gone some way to explain the varying conclusions on the effectiveness of TH in TBI by analysing the main subgroups.

Ongoing trials of therapeutic hypothermia for traumatic brain injury

There are two ongoing RCTs that are yet to be published: the POLAR RCT¹²⁶ and the RCT of Long-term Mild Hypothermia for Severe Traumatic Brain Injury trial (LTH-1).¹²⁷ Both author groups were contacted during the production of this systematic review.

The POLAR RCT is a neuroprotection study, the results of which may support the finding of this review that early hypothermia is beneficial.

In the earlier 2014 systematic review,¹¹⁰ the B-HYPO¹⁰⁷ investigators kindly provided preliminary data from their RCT. The full RCT has now been published and has been included in this updated systematic review.

Conclusions

Overall, this updated systematic review shows that, when high-quality studies of the use of TH in TBI are reviewed together, they show no significant differences in mortality, poor outcomes or new pneumonia; therefore, the use of TH is not evidenced. Conversely, the low-quality studies are more likely to show a benefit of TH in TBI. In addition, this review highlights the importance of fever control as, in those studies that included control groups with no temperature control, there was a higher rate of mortality than in those controlled to normothermia.

Key messages

- High-quality studies show no significant difference in mortality, poor outcomes or new pneumonia.
- When temperature in the control group is controlled normothermia, there is no difference in mortality.

Chapter 6 A biological effect or an imbalance of co-interventions? Exploratory analyses of the Eurotherm3235 Trial

Introduction

The Eurotherm3235 Trial was pragmatic and data collection was not overburdensome. We believe that this is one reason for the success of the trial; however, our data collection was not sufficiently comprehensive to allow investigation of possible mechanisms of the unexpected result. We are grateful to the National Institute for Health Research Health Technology Assessment programme for extending our funding to allow us to conduct a separate, retrospective study of the details of individual patient care in the main trial and mode of death, when appropriate. We considered this 'additional data collection' to be an important exercise for allowing full implementation of the trial results.

Background

Although early trials of TH after TBI showed that this treatment improved functional outcome, two recent multicentre trials, NABISH (National Acute Brain Injury Study: Hypothermia) and B-HYPO,^{76,107} have failed to confirm a neuroprotective effect. In a systematic review, Crossley *et al.*¹¹⁰ reported that TH might be beneficial in the treatment of TBI, although most of the positive trials that were included were of low quality and probably overestimated the effects of hypothermia. Madden and DeVon¹²⁸ showed that controlled normothermia, avoiding fever, improved functional outcomes, whereas hypothermia was associated with unfavourable outcomes. Additionally, three large, paediatric multicentre trials have not found evidence of benefit of TH, showing an increment in mortality in this population.^{129–131}

The Eurotherm3235 Trial was not designed to investigate why TH was associated with a poorer outcome; however, this relationship may arise because of either a biological effect of TH or an imbalance in co-interventions used in the hypothermia or control groups.

We therefore undertook a retrospective additional data collection exercise with the following aims:

- to assess the mode of death by treatment allocation
- to compare aspects of clinical management by treatment allocation including surgical intervention(s), medical treatments and drug dosages for management of raised ICP
- to compare the incidence of comorbidities and complications of care by treatment allocation
- to compare the available physiological data (not available in the original study) by treatment allocation.

Material and methods

Ethics approval for the collection of additional data through a bespoke case report form (CRF) was obtained from the Scotland Research Ethics Committee and the Bradford Research Ethics Committee in November 2015. A total of 47 centres in 18 countries that had randomised 387 participants from November 2009 to October 2014 were contacted. A total of 21 UK recruiting sites were invited to participate on 4 December 2015, whereas the 26 non-UK centres were required to obtain permission from their ethics/hospital committee prior to beginning participation.

The data collection started on 1 January 2016 and the deadline for completion of the CRFs was set to 31 July 2016. This was 6 years and 2 months after the beginning of the main trial and 1 year and 3 months after the last 6-month outcome assessment. Paper CRFs were used for the retrospective data collection and they were completed from the participant's medical notes, imaging and 24-hour ICU charts. There were 15 areas of interest, including comorbidities, (likely) cause of death and, for days 1–7, post randomisation information on medical and surgical interventions for raised ICP (ICP of > 20 mmHg), sedation and analgesia regimes, cardiovascular support, blood results and infection(s).

The additional data collection exercise provided sufficient information to calculate a modified and abbreviated sequential organ failure assessment (SOFA) to assess organ dysfunction. The full SOFA is composed of six domains, scoring respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems, graded from 0 to 4 depending on the degree of dysfunction/failure. For this exploratory analysis, we defined a modified SOFA excluding the respiratory and neurological domains. The rationale for this was that in the Eurotherm3235 Trial all participants were sedated (masking neurological assessment) and mechanically ventilated (affecting respiratory system SOFA) to control ICP at stage I. Formal assessment of GCS was not practical in many cases as a result of concerns about the likely effect of a sedation break on ICP. For the abbreviated SOFA, each of the remaining four organ domains were scored either as normal (0) or abnormal (1) and the sum of these was calculated. These scores were then used to characterise participants as having either minimal organ dysfunction (modified SOFA score of ≤ 1) or significant organ dysfunction (SOFA score of > 1).

Completed CRFs were sent by e-mail or post to the Eurotherm3235 Trial office at the Western General Hospital in Edinburgh. Eurotherm3235 Trial staff (Claire Battison, Trial Manager, and Irene Puddu, Research Fellow) worked closely with local clinicians to obtain complete and accurate data within the set time frame.

Statistical analysis

For all data collected, descriptive statistics by allocated treatment and dichotomised by GOSE outcome (favourable vs. unfavourable) were generated.

Results

Data

Responses were received from a total of 33 centres out of the 47 centres in the main trial, of which 16 (48%) were UK and 17 (52%) were non-UK sites. A total of 286 anonymised CRFs (UK, $n = 163$; and non-UK, $n = 123$) were returned by e-mail or post to the Eurotherm3235 Trial office by 31 July 2016. Data were returned on 143 participants randomised to TH and 143 participants randomised to the control groups. This distribution was similar to the main trial.

Demographics and baseline characteristics

The demographics of this sample were well matched between the TH and control group and were very similar to those of the main trial ITT population. *Table 13* shows that the baseline characteristics of the two 'additional data collection' groups were similar in all respects. Furthermore, the TH and control groups were well balanced for comorbidities (see *Table 13*).

The incidence of pre-ICU admission of secondary brain injuries because of either hypoxia [$n = 27$ (20.9%) in TH vs. $n = 17$ (13.2%) in the control group; $p = 0.136$] or hypotension [$n = 15$ (12.0%) in TH vs. $n = 11$ (8.6%) in the control group; $p = 0.493$] was not different between the groups. However, clinical signs of hypoxia were proportionally more frequent in the TH group ($n = 12$, 44.4%) than in the control group ($n = 1$, 6.3%), and blood gas evidence of hypoxia was more frequent in the control group [13 (48.2%) in TH vs. 13 (81.3%) in the control group; $p = 0.031$], although the absolute number of arterial gases identifying hypoxia were identical in both groups (see *Table 13*).

TABLE 13 Summary of baseline demographic, mechanism of injury, time from injury, clinical and radiological presentation, comorbidities and pre-ICU secondary insults data

| Data | Treatment group | | <i>p</i> -value |
|---|--|---------------------------|-----------------|
| | Hypothermia (<i>N</i> = 143) ^a | Control (<i>N</i> = 143) | |
| Characteristic | | | |
| Aged < 45 years, <i>n</i> (%) | 95 (66.4) | 95 (66.4) | 0.900 |
| Age (years), median (interquartile range) | 35 (24–49) | 36 (26–48) | 0.966 |
| Male, <i>n</i> (%) | 115 (80.4) | 120 (83.9) | 0.537 |
| Mechanism of injury, <i>n</i> (%) | | | |
| Road traffic accident: pedestrian | 17 (12.0) | 22 (15.4) | 0.319 |
| Road traffic accident: motor vehicle | 46 (32.4) | 34 (23.8) | |
| Cycling accident | 5 (3.5) | 9 (6.3) | |
| Fall | 62 (43.7) | 61 (42.7) | |
| Sports injury | 1 (0.7) | 0 (0.0) | |
| Assault | 11 (7.7) | 17 (11.9) | |
| Isolated TBI, <i>n</i> (%) | 88 (61.5) | 99 (69.2) | 0.214 |
| GCS motor score, <i>n</i> (%) | | | |
| 1 or 2 | 41 (28.7) | 35 (24.5) | 0.503 |
| 3–6 | 102 (71.3) | 108 (75.5) | |
| Pupillary response, <i>n</i> (%) | | | |
| Both reacting | 106 (74.1) | 107 (74.8) | 1.0 |
| One or neither reacting | 37 (25.9) | 36 (25.2) | |
| Marshall classification, <i>n</i> (%) | | | |
| Diffuse axonal injury I–III | 55 (38.5) | 58 (40.6) | 0.918 |
| Diffuse axonal injury IV | 16 (11.2) | 13 (9.1) | |
| Any lesion surgically removed | 32 (22.4) | 34 (23.8) | |
| High-density or mixed-density lesion | 40 (28.0) | 38 (26.6) | |
| At randomisation | | | |
| Time from injury ≥ 12 hours, <i>n</i> (%) | 130 (90.9) | 133 (93.0) | 0.664 |
| Intracranial pressure at randomisation (mmHg), median (interquartile range) | 24 (22–27) | 23 (22–26) | 0.473 |
| Core temperature at randomisation (°C), median (interquartile range) | 36.9 (36.4–37.4) | 37.1 (36.6–37.6) | 0.051 |
| Comorbidities | | | |
| Arthritis, <i>n</i> (%) | | | |
| Yes | 3 (2.2) | 5 (3.6) | 0.712 |
| No | 135 (97.8) | 132 (96.4) | |
| Osteoporosis, <i>n</i> (%) | | | |
| Yes | 1 (0.7) | 0 (0.0) | 0.997 |
| No | 138 (99.3) | 140 (100) | |
| Asthma, <i>n</i> (%) | | | |
| Yes | 8 (5.8) | 5 (3.6) | 0.561 |
| No | 129 (94.2) | 133 (96.4) | |
| | | | continued |

TABLE 13 Summary of baseline demographic, mechanism of injury, time from injury, clinical and radiological presentation, comorbidities and pre-ICU secondary insults data (*continued*)

| Data | Treatment group | | p-value |
|-----------------------------|------------------------------------|-------------------|---------|
| | Hypothermia (N = 143) ^a | Control (N = 143) | |
| COPD/emphysema, n (%) | | | |
| Yes | 6 (4.3) | 4 (2.9) | 0.739 |
| No | 133 (95.7) | 136 (97.1) | |
| Angina, n (%) | | | |
| Yes | 1 (0.7) | 1 (0.7) | 0.481 |
| No | 138 (99.3) | 139 (99.3) | |
| CCF, n (%) | | | |
| Yes | 4 (2.9) | 3 (2.1) | 0.992 |
| No | 135 (97.1) | 137 (97.9) | |
| MI, n (%) | | | |
| Yes | 3 (2.2) | 0 (0.0) | 0.243 |
| No | 136 (97.8) | 140 (100) | |
| Neurological disease, n (%) | | | |
| Yes | 6 (4.3) | 3 (2.1) | 0.491 |
| No | 133 (95.7) | 137 (97.9) | |
| Stroke/TIA, n (%) | | | |
| Yes | 1 (0.7) | 2 (1.4) | 0.995 |
| No | 138 (99.3) | 138 (98.6) | |
| PVD, n (%) | | | |
| Yes | 2 (1.4) | 2 (1.4) | 0.62 |
| No | 137 (98.6) | 138 (98.6) | |
| Diabetes mellitus, n (%) | | | |
| Yes | 8 (5.8) | 5 (3.6) | 0.561 |
| No | 131 (94.2) | 135 (96.4) | |
| GI disease, n (%) | | | |
| Yes | 5 (3.6) | 2 (1.4) | 0.438 |
| No | 134 (96.4) | 138 (98.6) | |
| Depression, n (%) | | | |
| Yes | 16 (11.5) | 12 (8.6) | 0.537 |
| No | 123 (88.5) | 128 (91.4) | |
| Anxiety, n (%) | | | |
| Yes | 6 (4.3) | 8 (5.7) | 0.795 |
| No | 133 (95.7) | 132 (94.3) | |
| Visual impairment, n (%) | | | |
| Yes | 1 (0.7) | 0 (0.0) | 0.997 |
| No | 138 (99.3) | 140 (100) | |
| Hearing impairment, n (%) | | | |
| Yes | 1 (0.7) | 1 (0.7) | 0.481 |
| No | 138 (99.3) | 139 (99.3) | |

TABLE 13 Summary of baseline demographic, mechanism of injury, time from injury, clinical and radiological presentation, comorbidities and pre-ICU secondary insults data (*continued*)

| | Treatment group | | |
|---|------------------------------------|-------------------|---------|
| Data | Hypothermia (N = 143) ^a | Control (N = 143) | p-value |
| Disc disease, n (%) | | | |
| Yes | 1 (0.7) | 2 (1.4) | 0.995 |
| No | 137 (99.3) | 137 (98.6) | |
| BMI of > 30 kg/m ² , n (%) | | | |
| Yes | 4 (2.9) | 6 (4.3) | 0.756 |
| No | 135 (97.1) | 134 (95.7) | |
| Secondary insults pre ICU admission | | | |
| Hypoxia, n (%) | | | |
| Yes | 27 (20.9) | 17 (13.2) | 0.136 |
| No | 102 (79.1) | 112 (86.8) | |
| Hypoxia detected, n (%) | | | |
| Arterial gases | 13 (48.2) | 13 (81.3) | 0.031 |
| Clinical signs | 12 (44.4) | 1 (6.3) | |
| Both | 2 (7.4) | 2 (12.5) | |
| Hypotension, n (%) | | | |
| Yes | 15 (12.0) | 11 (8.6) | 0.493 |
| No | 110 (88.0) | 117 (91.4) | |
| Hypotension detected, n (%) | | | |
| Blood pressure | 10 (55.6) | 7 (53.9) | 0.638 |
| Clinical signs | 1 (5.6) | 2 (15.4) | |
| Both | 7 (38.9) | 4 (30.8) | |
| BMI, body mass index; CCF, congestive cardiac failure; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; MI, myocardial infarction; PVD, peripheral vascular disease; TIA, transient ischaemic attack. | | | |
| Note | | | |
| a Participants may have no or multiple comorbidities. | | | |

Additional data collection sample mortality

Hypothermia was associated with a statistically significant increased risk of death at 6 months (*Figure 17*). In the additional data collection sample, a total of 78 participants died: 46 participants in the TH group (32.2%) and 32 participants in the control group (22.5%) (HR 1.624, 95% CI 1.025 to 2.573; $p = 0.0388$). These data were consistent with the ITT study population and suggest no reporting bias in this retrospective cohort.

Cause of death

Table 14 shows that the number of deaths due to brain stem death (BSD) was the same in both groups, but because of other causes of death with TH, BSD represented a greater proportion in the control group [12 (28.6%) deaths in TH vs. 12 (42.3%) deaths in control group]. In the TH group, pathologies with a strong inflammatory component, including multiorgan failure (MOF), infection and acute respiratory distress syndrome (ARDS), were more commonly attributed to causing death in the TH group [15 (35.7%) deaths in TH vs. 5 (19.1%) deaths in control group; $p = 0.618$].

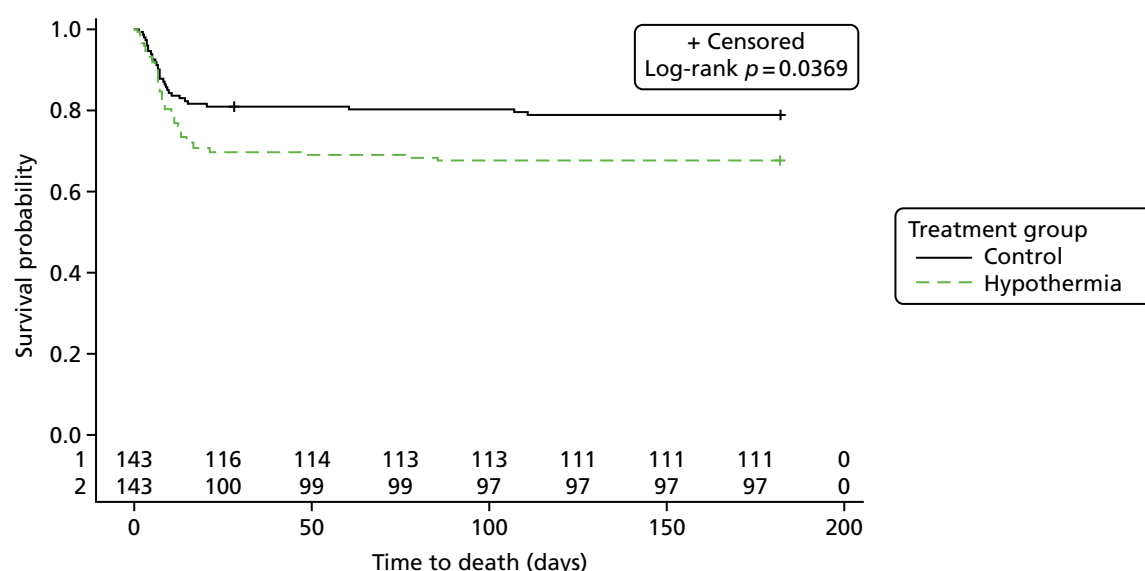


FIGURE 17 Survival curve between randomisation and 6 months by treatment allocation in the additional data collection cohort.

TABLE 14 Primary outcome of the additional data collection population: likely causes of death

| Cause of Death | Treatment group, n (%) | | p-value |
|-------------------------|------------------------|-----------|---------|
| | Hypothermia | Control | |
| BSD | 12 (28.6) | 11 (42.3) | 0.618 |
| MOF/sepsis/ARDS | 15 (35.7) | 5 (19.2) | |
| Neurological/withdrawal | 11 (26.2) | 7 (26.9) | |
| Cardiac event | 2 (4.8) | 2 (7.7) | |
| Other | 2 (4.8) | 1 (3.9) | |

Clinical management and interventions

Intracranial pressure management: medical therapy

The main trial results showed that the mean daily ICP was similar in the two groups. During the first 4 days after randomisation, there were fewer failures of stage II therapy to control ICP in TH than in the control group (57 vs. 84 participants). In this exploratory analysis, the use of medical treatments to control ICP was similar in both groups over days 1–7 after randomisation: 128 participants (92.1%) in the TH group received medical treatments for raised ICP compared with 124 participants (91.9%) in the control group ($p = 0.88$) (see Table 15). There was no significant difference in the average number of participants treated with hypertonic saline per day [mean 35.0 (SD 6.2) in the TH group vs. mean 39.6 (SD 10.9) in the control group; $p = 0.353$] or the average number of daily treatments given [mean 1.9 (SD 0.7) in TH group vs. mean 2.5 (SD 0.9) in the control group; $p = 0.15$]. Similarly, for mannitol, the average number of participants treated (mean 37.0 (SD 9.4) in the TH group vs. [mean 43.3 (SD 16.0) in the control group; $p = 0.388$]) and the average number of daily treatments [2.0 (2.0–2.0) in the TH group vs. 2.0 (2.0–2.0) in the control group; $p = 0.71$] were not significantly different. The average number of daily treatments with furosemide was statistically significantly higher in the control group than the TH group [mean 1.2 (SD 0.4) in the TH group vs. mean 1.9 (SD 0.4) in the control group; $p = 0.004$], but there was no difference in the average number of participants treated per day [mean 13.3 (SD 4.3) in the TH group vs. mean 15.7 (SD 5.6) in the control group; $p = 0.384$] (Table 15).

Intracranial pressure management: surgical treatment

The surgical management of raised ICP was also similar between groups. The number of participants undergoing decompressive craniectomy before randomisation was 21 (15.4%) in the TH group, compared

TABLE 15 Medical and surgical management for raised ICP after randomisation

| | Treatment group | | |
|---|-----------------|---------------|-----------------|
| Management | Hypothermia | Control | <i>p</i> -value |
| Treatment for raised ICP, mean (SD) | | | |
| Yes | 128 (92.1) | 124 (91.9) | 0.88 |
| No | 11 (7.9) | 11 (8.1) | |
| ICP treatments | | | |
| Hypertonic saline, mean (SD) | 35.0 (6.2) | 39.6 (10.9) | 0.353 |
| Hypertonic saline (treatments/day), mean (SD) | 1.9 (0.7) | 2.5 (0.9) | 0.15 |
| Mannitol, median (SD) | 37.0 (9.4) | 43.3 (16) | 0.388 |
| Mannitol (treatments/day) (range) | 2.0 (2.0–2.0) | 2.0 (2.0–2.0) | 0.71 |
| Frusemide, mean (SD) | 13.3 (4.3) | 15.7 (5.6) | 0.384 |
| Frusemide (treatments/day), mean (SD) | 1.2 (0.4) | 1.9 (0.4) | 0.004 |
| Decompressive craniectomy, mean (SD) | | | |
| Before randomisation | | | |
| Yes | 21 (15.4) | 23 (16.4) | 0.952 |
| No | 115 (84.6) | 117 (83.6) | |
| After randomisation | | | |
| Yes | 34 (24.8) | 37 (26.2) | 0.893 |
| No | 103 (75.2) | 104 (73.8) | |
| Craniectomy type, mean (SD) | | | |
| Hemicraniectomy | 29 (58.0) | 37 (64.9) | 0.593 |
| Bifrontal | 21 (42.0) | 20 (35.1) | |

with 23 (16.3%) in the control group ($p = 0.952$), and after randomisation was 34 (24.8%) in the TH group, compared with 37 (26.2%) in the control group ($p = 0.893$) (see *Table 15*). The proportion of participants undergoing hemicraniectomy was slightly greater in the control group than in the TH group [29 (58.0%) in TH group vs. 37 (64.9%) in the control group], whereas bifrontal craniectomy was more common in the TH group than in the control group [21 (42.0%) in the TH group vs. 20 (35.1%) in the control group]. Only one participant in each group underwent decompressive craniectomy before and after randomisation. However, these distributions were not significantly different between the groups ($p = 0.593$) (see *Table 15*).

Follow-up computed tomography

Follow-up CT was performed in significantly more participants in the control group than the TH group: 105 (80.8%) in TH group compared with 120 (90.2%) in the control group ($p = 0.045$) (*Table 16*). The distribution of Marshall scores based on the second CT scan was similar in both groups, with no statistically significant differences ($p = 0.323$). In both the TH and CG groups of the additional collection exercise, type II diffuse injury and high- or mixed-density lesion not evacuated were the most common pathologies observed [26 participants (24.8%) in the TH group vs. 31 participants (26.7%) in the control group, for both] (see *Table 16*). For both the TH group and the control group, the distribution of Marshall scores with the type of decompressive craniectomy was not significantly different ($p = 0.506$ in the TH group; $p = 0.189$ in the control group) (see *Table 16*). In the TH group, removable lesions were most frequently associated with both hemicraniectomy and bifrontal craniectomy [10 participants (41.7%) had a hemicraniectomy vs. five participants (38.5%) who had a bifrontal procedure]. By contrast, in the control group, removable lesions were most commonly associated with hemicraniectomy (14 participants, 46.7%), but a type II diffuse injury was slightly more common in those receiving bifrontal craniectomy (four participants,

TABLE 16 Marshall classification on follow-up CT and type of craniectomy

| CBT classification of TBI lesion | Craniectomy type, <i>n</i> (%) | | <i>p</i> -value |
|---|--------------------------------|------------|-----------------|
| | Hypothermia | Control | |
| Follow-up CT | | | |
| Yes | 105 (80.8) | 120 (90.2) | 0.045 |
| No | 25 (19.2) | 13 (9.8) | |
| Marshall classification | | | |
| Diffuse injury I (no visible pathology) | 2 (1.9) | 2 (1.7) | 0.323 |
| Diffuse injury II | 26 (24.8) | 31 (26.7) | |
| Diffuse injury III (swelling) | 18 (17.1) | 8 (6.9) | |
| Diffuse injury IV (shift) | 13 (12.4) | 16 (13.8) | |
| Any lesion surgically removed | 20 (19.0) | 28 (24.1) | |
| High- or mixed-density lesion | 26 (24.8) | 31 (26.7) | |
| | Hypothermia, <i>n</i> (%) | | |
| | Hemicraniectomy | Bifrontal | |
| Marshall classification | | | |
| Diffuse injury I (no visible pathology) | 1 (4.2) | 0 (0.0) | 0.506 |
| Diffuse injury II | 3 (12.5) | 2 (15.4) | |
| Diffuse injury III (swelling) | 1 (4.2) | 3 (23.1) | |
| Diffuse injury IV (shift) | 4 (16.7) | 2 (15.4) | |
| Any lesion surgically removed | 10 (41.7) | 5 (38.5) | |
| High- or mixed-density lesion | 5 (20.8) | 1 (7.7) | |
| | Control, <i>n</i> (%) | | |
| | Hemicraniectomy | Bifrontal | |
| Marshall classification | | | |
| Diffuse injury I (no visible pathology) | 0 (0.0) | 1 (7.1) | 0.189 |
| Diffuse injury II | 2 (6.7) | 4 (28.6) | |
| Diffuse injury III (swelling) | 3 (10.0) | 1 (7.1) | |
| Diffuse injury IV (shift) | 5 (16.7) | 3 (21.4) | |
| Any lesion surgically removed | 14 (46.7) | 3 (21.4) | |
| High- or mixed-density lesion | 6 (20.0) | 2 (14.3) | |
| | Treatment group, <i>n</i> (%) | | |
| | Hypothermia | Control | |
| Marshall classification | | | |
| Diffuse injury I (no visible pathology) | 1 (4.2) | 0 (0.0) | 0.787 |
| Diffuse injury II | 3 (12.5) | 2 (6.7) | |
| Diffuse injury III (swelling) | 1 (4.2) | 3 (10.0) | |
| Diffuse injury IV (shift) | 4 (16.7) | 5 (16.7) | |
| Any lesion surgically removed | 10 (41.7) | 14 (46.7) | |
| High- or mixed-density lesion | 5 (20.8) | 6 (20.0) | |

TABLE 16 Marshall classification on follow-up CT and type of craniectomy (*continued*)

| | Bifrontal: treatment group, <i>n</i> (%) | | <i>p</i> -value |
|---|--|----------|-----------------|
| | Hypothermia | Control | |
| Marshall classification | | | |
| Diffuse injury I (no visible pathology) | 0 (0.0) | 1 (7.1) | 0.598 |
| Diffuse injury II | 2 (15.4) | 4 (28.6) | |
| Diffuse injury III (swelling) | 3 (23.1) | 1 (7.1) | |
| Diffuse injury IV (shift) | 2 (15.4) | 3 (21.4) | |
| Any lesion surgically removed | 5 (38.5) | 3 (21.4) | |
| High- or mixed-density lesion | 1 (7.7) | 2 (14.3) | |

28.6%). For both hemicraniectomy and bifrontal craniectomy, the distribution of Marshall scores by treatment allocation was also not significantly different ($p = 0.787$ for hemicraniectomy; $p = 0.598$ for bifrontal craniectomy) (see *Table 16*).

Sedation and analgesia

Midazolam infusion was used more often in the TH group: the mean number of participants per day was 96.0 (SD 12.8) in the TH group compared with 78.7 (SD 16.0) in the control group ($p = 0.046$), with the same hourly infusion rate in both groups [median 10.0 (IQR 10.0–10.0) mg/hour in the TH group vs. median 10.0 (IQR 10.0–10.0) mg/hour in the control group; $p = 0.71$] (*Table 16*). Alfentanil and fentanyl were the most commonly used opioids in all centres. The number of participants receiving alfentanil each day was higher in the TH group than in the control group [mean 37.1 (SD 4.7) in the TH group vs. mean 27.7 (SD 5.2) in the control group; $p = 0.004$], but the hourly dose was the same in both groups [median 2.5 (IQR 2.5–2.5) mg/hour in the TH group vs. median 2.5 (IQR 2.5–2.5) mg/hour in the control group; $p = 1.0$]. In contrast, the number of participants treated per day with fentanyl was not significantly different between groups [mean 56.0 (SD 6.9) in the TH group vs. mean 58.4 (SD 7.7) in the control group; $p = 0.545$] or the hourly dose [median 250 (IQR 250–250) µg/h in the TH group vs. median 250 (IQR 250–250) µg/h in the control group; $p = 0.71$] (see *Table 17*).

The average number of participants sedated with propofol per day was similar in both groups: a total of 89.9 (SD 14.2) participants in the TH group, compared with 79.1 (SD 17.8) participants in the control group ($p = 0.236$). The mean daily dose of 4615.3 (SD 658.8) mg/day in the TH group compared with 4801.4 (SD 657.0) mg/day in the control group ($p = 0.606$) (see *Table 15*). Correcting the daily dose for the participants' weight did not reveal any between-group difference: 60.0 (SD 8.6) mg/kg/day in the TH group compared with 62.7 (SD 5.4) mg/kg/day in the control group ($p = 0.5$). After adjustment for age, post resuscitation GCS motor component, time from injury and pupil reactivity, no significant differences in the average daily dose of propofol in each group were found. A potentially toxic level infusion rate of propofol (> 5 mg/kg/hour) was used in a few participants per day in both groups [median 3.0 participants (IQR 2.3–5.3) in the TH group and median 4.0 participants (IQR 3.0–4.0) in the control group; $p = 0.535$].

Atracurium was the predominant neuromuscular blocking agent used in all 33 centres. The number of participants receiving atracurium was significantly greater in the TH group [mean 31.1 (SD 6.8)] than in the control group [mean 22.0 (SD 4.5)] ($p = 0.012$) after randomisation. However, the median hourly infusion rate was slightly higher in the control group than in the TH group: median 50.0 (IQR 50.0–50.0) mg/hour in the TH group, compared with median 60.0 (IQR 50.8–60.0) mg/hour in the control group ($p = 0.017$) (see *Table 17*).

TABLE 17 Sedation and analgesia used after randomisation

| Intervention | Treatment group | | p-value |
|--|---------------------|---------------------|---------|
| | Hypothermia | Control | |
| Sedation | | | |
| Midazolam, mean (SD) | 96.0 (12.8) | 78.7 (16.0) | 0.046 |
| Midazolam (mg/hour), median (IQR) | 10.0 (10.0–10.0) | 10.0 (10.0–10.0) | 0.71 |
| Analgesia | | | |
| Fentanyl, mean (SD) | 56 (6.9) | 58.4 (7.7) | 0.545 |
| Fentanyl (µg/hour), median (IQR) | 250.0 (250.0–250.0) | 250.0 (250.0–250.0) | 0.71 |
| Alfentanil, mean (SD) | 37.1 (4.7) | 27.7 (5.2) | 0.004 |
| Alfentanil (mg/hour), median (IQR) | 2.5 (2.5–2.5) | 2.5 (2.5–2.5) | 1 |
| Sedation, mean (SD) | | | |
| Propofol | 89.9 (14.2) | 79.1 (17.8) | 0.236 |
| Propofol (mg/day) | 4615.3 (658.8) | 4801.4 (657.0) | 0.606 |
| Propofol (mg/kg/day), mean (SD) | 60.0 (8.6) | 62.7 (5.4) | 0.5 |
| Propofol (mg/kg/hour), mean (SD) | 2.5 (0.4) | 2.6 (0.2) | 0.495 |
| Propofol number reaching toxic dose (> 5 mg/kg/hour), median (IQR) | 3.0 (2.3–5.3) | 4.0 (3.0–4.0) | 0.535 |
| NMB | | | |
| Atracurium, mean (SD) | 31.1 (6.8) | 22.0 (4.5) | 0.012 |
| Atracurium (mg/hour), median (IQR) | 50.0 (50.0–50.0) | 60.0 (50.8–60.0) | 0.017 |
| NMB, neuromuscular blocking agent. | | | |

NMB, neuromuscular blocking agent.

Cardiovascular support

The use of drugs to support the cardiovascular system was greater in the TH group than in the control group. The average number of participants receiving noradrenaline per day [mean 95.4 (SD 12.9) in the TH group vs. mean 78.1 (SD 18.7) in the control group] and the daily infusion rate [mean 15.3 (SD 3.5) mg/day in the TH group vs. mean 12.2 (SD 2.5) mg/day in the control group] were not significantly different ($p = 0.067$ and $p = 0.078$, respectively) (Table 18). Dobutamine was used in more TH participants [mean 7.3 (SD 3.1) participants/day] than control group participants [mean 2.3 (SD 1.0) participants/day] ($p = 0.002$), although the daily infusion rates were similar [median 292.5 (IQR 221.3–466.9) mg/day in the TH group vs. median 315.0 (IQR 193.9–441.9) mg/day in the control group; $p = 0.71$]. Similarly, more participants received daily vasopressin in the TH group [mean 5.7 (SD 2.4)] than in the control group [mean 1.9 (SD 0.9)] ($p = 0.002$),

TABLE 18 Cardiovascular support after randomisation

| Cardiovascular support | Treatment group | | <i>p</i> -value |
|---------------------------------------|---------------------|---------------------|-----------------|
| | Hypothermia | Control | |
| Noradrenaline, mean (SD) | 95.4 (12.9) | 78.1 (18.7) | 0.067 |
| Noradrenaline (mg/day), mean (SD) | 15.3 (3.5) | 12.2 (2.5) | 0.078 |
| Dobutamine, mean (SD) | 7.3 (3.1) | 2.3 (1.0) | 0.002 |
| Dobutamine (mg/day), median (IQR) | 292.5 (221.3–466.9) | 315.0 (193.9–441.9) | 0.71 |
| Vasopressin, mean (SD) | 5.7 (2.4) | 1.9 (0.9) | 0.002 |
| Vasopressin (units/day), median (IQR) | 24.9 (16.7–31.6) | 60.4 (6.0–778.8) | 0.71 |

with a daily dose of median 24.9 (IQR 16.7–31.6) U/day in the TH group compared with median 60.4 (IQR 6.0–778.8) U/day in the control group ($p = 0.71$) (see *Table 18*).

Steroids

The number of participants receiving steroids was greater in the TH group [23 (17.8%)] than in the control group [9 (6.7%)] ($p = 0.01$) (*Table 19*). The most frequently used steroid was hydrocortisone: 20 participants, with a median daily dose of 100 mg (range 25–600 mg), used this steroid in the TH group compared with six participants, with a median daily dose of 125 mg (range 50–200 mg), in the control group.

Fluid balance

Daily fluid balance was similar in both groups. The number of participants per day with a positive fluid balance [mean 84.4 participants (SD 19.2) in the TH group vs. mean 87.3 (SD 17.0) in the control group; $p = 0.773$] or negative fluid balance [mean 32.9 (SD 13.9) in the TH group vs. mean 30.9 (SD 11.3) in the control group; $p = 0.773$] was similar. Average daily fluid balance was also similar between the groups [mean 781.7 (SD 409.9) ml in TH vs. mean 657.3 (SD 406.6) ml in control group; $p = 0.579$] (*Table 19*).

Laboratory results and organ failure

There were no significant differences in the average daily haemoglobin [mean 102.4 (SD 2.8) g/l in the TH group vs. mean 102.8 (SD 4.6) g/l in the control group; $p = 0.839$], haematocrit [mean 0.3 (SD 0.0) in the TH group vs. mean 0.3 (SD 0.0) in the control group; $p = 0.139$] or platelet count [mean $163.1 \times 10^9/l$ in the TH group vs. mean $195.5 \times 10^9/l$ in the control group; $p = 0.053$] between the two groups (*Table 20*).

Liver function was not significantly different in the two groups. There were no significant differences between the two groups for average daily bilirubin [mean 8.2 (SD 0.7) $\mu\text{mol/l}$ in the TH group vs. mean 8.3 (SD 1.3) $\mu\text{mol/l}$ in the control group; $p = 0.832$], alanine transaminase (ALT) [median 32.0 (IQR 29.3–41.5) U/l in the TH group vs. median 30.5 (IQR 29.0–44.8) U/l in the control group; $p = 1.0$] and albumin [median 25.8 (IQR 25.5–27.4) g/l in the TH group vs. median 26.9 (IQR 26.5–28.5) g/l in the control group; $p = 0.128$] (see *Table 20*). Average daily APTT (activated partial thromboplastin time) [mean 33.2 (SD 2.1) seconds in the TH group vs. mean 31.2 (SD 1.3) seconds in the control group; $p = 0.046$] and APTTr (activated partial thromboplastin time ratio) [mean 1.2 (SD 0.1) in the TH group vs. mean 1.1 (SD 0.0) in the control group; $p = 0.037$] were significantly increased in the TH group.

Renal function was not significantly different in the two groups for average daily serum urea [mean 4.30 (SD 0.83) mmol/l in the TH group vs. mean 4.33 (SD 1.0) mmol/l in the control group; $p = 0.959$] or creatinine [mean 54.9 (SD 4.9) $\mu\text{mol/l}$ in the TH group vs. mean 57.9 (SD 3.3) $\mu\text{mol/l}$ in the control group; $p = 0.205$] (see *Table 20*). Electrolyte concentrations were identical in the TH and control groups: serum

TABLE 19 Corticosteroids prescribed during ICU admission and fluid balance after randomisation

| Intervention | Treatment group | | <i>p</i> -value |
|--|-----------------|---------------|-----------------|
| | Hypothermia | Control | |
| Receiving steroids, <i>n</i> (%) | | | |
| Yes | 23 (17.8) | 9 (6.7) | 0.01 |
| No | 106 (82.2) | 125 (93.3) | |
| Receiving hydrocortisone, <i>n</i> (%) | 2.9 (3.19) | 0.9 (0.90) | 0.136 |
| Fluid balance during randomisation | | | |
| Patients with a positive daily balance, <i>n</i> (%) | 84.4 (19.2) | 87.3 (17.0) | 0.773 |
| Patients with a negative daily balance, <i>n</i> (%) | 32.9 (13.9) | 30.9 (11.3) | 0.773 |
| Fluid balance (ml/day) mean (SD) | 781.7 (409.9) | 657.3 (406.6) | 0.579 |

TABLE 20 Laboratory results at randomisation

| Analysis | Treatment group | | p-value |
|---|---------------------|---------------------|---------|
| | Hypothermia | Control | |
| Haemoglobin (g/l), mean (SD) | 102.4 (2.8) | 102.8 (4.6) | 0.839 |
| Haematocrit (%), mean (SD) | 0.3 (0.0) | 0.3 (0.0) | 0.139 |
| White cell count ($\times 10^9/l$), mean (SD) | 9.9 (0.9) | 11.0 (0.7) | 0.031 |
| Neutrophils ($\times 10^9/l$), mean (SD) | 7.8 (0.6) | 9.0 (0.7) | 0.005 |
| Platelets ($\times 10^9/l$), mean (SD) | 163.1 (15.2) | 195.5 (36.9) | 0.053 |
| APTT (seconds), mean (SD) | 33.2 (2.1) | 31.2 (1.3) | 0.046 |
| APTT _r , mean (SD) | 1.2 (0.1) | 1.1 (0.0) | 0.037 |
| Urea (mmol/l), mean (SD) | 4.30 (0.83) | 4.33 (1.00) | 0.959 |
| Sodium (mmol/l), median (range) | 145.2 (144.2–145.4) | 145.0 (142.8–145.6) | 0.62 |
| Potassium (mmol/l), mean (SD) | 4.03 (0.14) | 4.03 (0.11) | 1 |
| Creatinine ($\mu\text{mol/l}$), mean (SD) | 54.9 (4.9) | 57.9 (3.3) | 0.205 |
| Bilirubin ($\mu\text{mol/l}$), mean (SD) | 8.22 (0.65) | 8.34 (1.29) | 0.832 |
| ALT (U/l), median (range) | 32.0 (29.3–41.5) | 30.5 (29.0–44.8) | 1 |
| Alkaline phosphatase (U/l), mean (SD) | 81.9 (21.1) | 85.5 (20.1) | 0.751 |
| Calcium (mmol/l), mean (SD) | 2.04 (0.04) | 2.08 (0.08) | 0.232 |
| Albumin (g/l), median (range) | 25.8 (25.5–27.4) | 26.9 (26.5–28.5) | 0.128 |
| Phosphate (mmol/l), mean (SD) | 1.10 (0.17) | 1.04 (0.11) | 0.444 |
| Magnesium (mmol/l), mean (SD) | 0.83 (0.02) | 0.85 (0.03) | 0.269 |
| C-reactive protein (mg/l), mean (SD) | 148.8 (31.9) | 160.4 (31.9) | 0.511 |
| Bicarbonate (mmol/l), mean (SD) | 23.0 (0.7) | 23.6 (0.5) | 0.101 |
| Lactate (mmol/l), mean (SD) | 1.20 (0.10) | 1.06 (0.11) | 0.027 |

APTT, activated partial thromboplastin time; APTT_r, activated partial thromboplastic time ratio.

sodium was median 145.2 (range 144.2–145.4) mmol/l in the TH group, compared with median 145.0 (range 142.8–145.6) mmol/l in the control group ($p = 0.62$) and potassium was mean 4.03 (SD 0.14) mmol/l in the TH group, compared with mean 4.03 (SD 0.11) mmol/l in the control group; $p = 1$].

There was no difference in the number of participants requiring renal replacement therapy (RRT). Seven participants (5.5%) in the TH group required RRT, compared with three participants (2.4%) in the control group ($p = 0.33$) (see Table 20). Evidence of rhabdomyolysis was reported in the same number of participants in each group [11 (9.1%) in the TH group vs. 11 (8.9%) in the control group; $p = 0.87$]. Additionally, elevated levels of creatine kinase and/or troponin T were reported in a similar proportion of participants across the two groups [37 (33.9%) in the TH group vs. 30 (28.6%) in the control group; $p = 0.484$]. The average serum creatinine kinase level was median 753 (IQR 505–1280) U/l in the TH group, compared with median 1013 (IQR 606–1554) U/l in the control group ($p = 0.336$), and the troponin T level was median 41.0 (IQR 10.0–142.0) ng/l in the TH group, compared with median 15.0 (IQR 3.755–38.3) ng/l in the control group ($p = 0.46$).

Acid–base estimation

Metabolic acidosis was reported significantly more often in the TH group than in the control group [45 participants (36.9%) in the TH group vs. 27 participants (22.1%) in the control group; $p = 0.017$], as was the use of an infusion of bicarbonate [17 (13.7%) in the TH group vs. 5 (4.2%) in the control group;

$p = 0.018$]. Average daily lactate concentrations were significantly greater in the TH group than in the control group [mean 1.2 (SD 0.1) mmol/l in the TH group vs. mean 1.1 (SD 0.1) mmol/l in the control group; $p = 0.027$], although serum bicarbonate concentrations were similar in both groups [mean 23.0 (SD 0.7) mmol/l in the TH group vs. mean 23.6 (SD 0.5) mmol/l in the control group; $p = 0.10$].

Organ dysfunction

Organ dysfunction was quantified using a modified abbreviated SOFA score. All analyses were made comparing minimal (SOFA score of ≤ 1) with significant (SOFA score of > 1) organ dysfunction. There was no significant difference in the distribution of SOFA scores between the TH group and the control group; 47 participants (32.9%) in the TH group and 55 participants (38.5%) in the control group had a SOFA score of ≤ 1 , and 96 participants (67.1%) in the TH group and 88 participants (61.5%) in the control group had a SOFA score of > 1 ($p = 0.388$) (Table 21). In the TH group, there were significantly more participants

TABLE 21 Complications and organ dysfunction after randomisation and organ dysfunction quantified using a modified abbreviated SOFA score

| Complications | Treatment group | | <i>p</i> -value |
|--|---|-----------------|-----------------|
| | Hypothermia | Control | |
| Haemofiltration, <i>n</i> (%) | | | |
| Yes | 7 (5.5) | 3 (2.4) | 0.333 |
| No | 120 (94.5) | 124 (97.6) | |
| Rhabdomyolysis, <i>n</i> (%) | | | |
| Yes | 11 (9.1) | 11 (8.9) | 0.87 |
| No | 110 (90.9) | 113 (91.1) | |
| Metabolic acidosis, <i>n</i> (%) | | | |
| Yes | 45 (36.9) | 27 (22.1) | 0.017 |
| No | 77 (63.1) | 95 (77.9) | |
| Bicarbonate infusion, <i>n</i> (%) | | | |
| Yes | 17 (13.7) | 5 (4.2) | 0.018 |
| No | 107 (86.3) | 114 (95.8) | |
| Troponin and/or CK elevation, <i>n</i> (%) | | | |
| Yes | 37 (33.9) | 30 (28.6) | 0.484 |
| No | 72 (66.1) | 75 (71.4) | |
| CK (units/l) <i>n</i> = 35/29, mean (range) | 769 (505–1478) | 1004 (606–1554) | – |
| Troponin (ng/l) <i>n</i> = 9/3, mean (range) | 41.0 (10.0–133.0) | 15.0 (0.0–46.0) | – |
| SOFA of ≤ 1, <i>n</i> (%) | 47 (32.9) | 55 (38.5) | 0.388 |
| SOFA of > 1, <i>n</i> (%) | 96 (67.1) | 88 (61.5) | |
| | SOFA score and survival – hypothermia | | |
| | Died | Survived | |
| SOFA of ≤ 1, <i>n</i> (%) | 7 (15.2) | 40 (41.2) | 0.004 |
| SOFA of > 1, <i>n</i> (%) | 39 (84.8) | 57 (58.8) | |
| | SOFA score and survival – control group | | |
| | Died | Survived | |
| SOFA of ≤ 1, <i>n</i> (%) | 11 (34.4) | 44 (40.0) | 0.712 |
| SOFA of > 1, <i>n</i> (%) | 21 (65.6) | 66 (60.0) | |
| CK, creatine kinase. | | | |

CK, creatine kinase.

who died with a SOFA score of > 1 [39 (84.8%) died vs. 57 (58.8%) survived] than with a SOFA score of ≤ 1 [7 (15.2%) died vs. 40 (41.2%) survived] ($p = 0.004$). This was not seen in the control group: 21 participants (65.6%) died compared with 66 participants (60.0%) survived with a SOFA score of > 1 , and 11 participants (34.4%) died compared with 44 participants (40.0%) survived with a SOFA score of ≤ 1 ($p = 0.712$). The distribution of SOFA scores was not significantly different for the dichotomised GOSE in either the TH group [73 (71.6%) unfavourable vs. 23 (59.0%) favourable with a SOFA score of > 1 , and 29 (28.4%) poor vs. 16 (41.0%) good outcome with a SOFA score of ≤ 1 ; $p = 0.218$] or the control group [53 (60.2%) poor vs. 33 (62.3%) good outcome with a SOFA score of > 1 and 35 (39.8%) poor vs. 20 (37.7%) good outcome with a SOFA score of ≤ 1 ; $p = 0.951$].

Immunity and infection

Therapeutic hypothermia was associated with a significantly lower average daily leucocyte count [mean 9.9 (SD 0.9) $\times 10^9/l$ in the TH group vs. 11.0 (SD 0.7) $\times 10^9/l$ in the control group; $p = 0.031$]. Similarly, the neutrophil count was also reduced [mean 7.8 (SD 0.6) $\times 10^9/l$ in the TH group vs. mean 9.0 (SD 0.7) $\times 10^9/l$ in the control group; $p = 0.005$]. However, there was no statistically significant difference between the two groups for average daily C-reactive protein [mean 148.8 (SD 31.9) mg/l in the TH group vs. mean 160.4 (SD 31.9) mg/l in the control group; $p = 0.511$].

The number of participants suspected of having infection was similar over days 1–7 of data collection [111 (81.6%) in the TH group vs. 106 (78.5%) in the control group; $p = 0.627$]. Confirmed infections were also similar [98 (79.0%) in the TH group vs. 94 (77.0%) in the control group; $p = 0.825$] (Table 22). Pneumonia was the most common infection in both groups, although there was no significant difference in the number of episodes between the two groups [84 (58.7%) episodes in the TH group vs. 78 (54.5%) in the control group; $p = 0.551$]. Endotracheal aspiration was the technique most frequently used to confirm a respiratory infection [35 participants (44.3%) in the TH group vs. 29 participants (40.8%) in the control group; $p = 0.754$]. There was no significant difference between the two groups in the number of participants who received antibiotics [116 (89.2%) in the TH group vs. 113 (87.6%) in the control group; $p = 0.828$].

Coenrolment

The number of participants coenrolled in other trials was similar in the two groups: 16 out of 143 participants (11.4%) in the TH group and 12 out of 143 participants (8.6%) in the control group ($p = 0.55$). The distribution of trials to which participants were coenrolled was not different. Coenrolment was not more frequent in non-survivors than in survivors in either the TH group [5 (11.1%) non-survivors vs. 11 (11.6%) survivors; $p = 0.839$] or the control group [3 (9.7%) non-survivors vs. 8 (7.4%) survivors; $p = 0.972$]. Similarly, coenrolment was not more common in those participants with an unfavourable outcome by GOSE in the TH group [11 (11.2%) unfavourable outcome vs. 3 (7.9%) good outcome; $p = 0.796$] or the control group [7 (8.2%) poor outcome vs. 4 (7.7%) good outcome; $p = 0.833$].

Method of cooling

The majority of participants were cooled with an automated device and surface cooling; Blanketrol® (Patient Temperature Management Solutions, Cincinnati, OH, USA) and ARCTIC SUN® 5000 Temperature Management System (Bard Medical Division, Covington, GA, USA) were the most commonly used devices (58.2% of the TH group sample), although a small percentage of participants were cooled with an intravascular device (ZOLL®; ZOLL, Pittsburgh, PA, USA) (23.9% of the TH group sample).

Unfavourable outcome at 6 months by GOSE was not associated with the type of cooling device used ($p = 0.441$).

TABLE 22 Infection and antibiotic usage after randomisation

| | Treatment group, <i>n</i> (%) | | |
|--|-------------------------------|------------|-----------------|
| Intervention | Hypothermia | Control | <i>p</i> -value |
| Suspected infection | | | |
| Yes | 111 (81.6) | 106 (78.5) | 0.627 |
| No | 25 (18.4) | 29 (21.5) | |
| Confirmed infection | | | |
| Yes | 98 (79.0) | 94 (77.0) | 0.825 |
| No | 26 (21.0) | 28 (23.0) | |
| Respiratory infection | | | |
| Yes | 84 (58.7) | 78 (54.5) | 0.551 |
| No | 59 (41.3) | 65 (45.5) | |
| Respiratory sample type | | | |
| Formal bronchoalveolar lavage | 19 (24.1) | 16 (22.5) | 0.754 |
| Mini bronchoalveolar lavage | 5 (6.3) | 8 (11.3) | |
| Endotracheal aspiration | 35 (44.3) | 29 (40.8) | |
| Sputum | 20 (25.3) | 18 (25.4) | |
| Infections | | | |
| Respiratory infection | | | |
| Yes | 84 (58.7) | 78 (54.5) | 0.551 |
| No | 59 (41.3) | 65 (45.5) | |
| Urinary infection | | | |
| Yes | 4 (2.8) | 9 (6.3) | 0.256 |
| No | 139 (97.2) | 134 (93.7) | |
| Catheter-related bloodstream infection | | | |
| Yes | 4 (2.8) | 5 (3.5) | 0.756 |
| No | 139 (97.2) | 138 (96.5) | |
| Sepsis of uncertain origin | | | |
| Yes | 2 (1.4) | 1 (0.7) | 1 |
| No | 141 (98.6) | 142 (99.3) | |
| Other infection | | | |
| Yes | 8 (5.6) | 7 (4.9) | 1 |
| No | 135 (94.4) | 136 (95.1) | |
| Antibiotics | | | |
| Antibiotics prescribed | | | |
| Yes | 116 (89.2) | 13 (87.6) | 0.828 |
| No | 14 (10.8) | 16 (12.4) | |

Discussion

This exploratory analysis collected additional information not considered in the original Eurotherm3235 Trial in order to explore possible reasons for the original trial results. Consistent with the ITT population, analysis of this additional data sample also showed that there was a statistically significant increase in the mortality within 6 months of randomisation in the hypothermia group. Treatment allocation, demographics and outcomes were similar to the ITT population.

The main observation that stands out from these results is that hypothermia was associated with an excess number of deaths as a consequence of sepsis/ARDS/MOF. In the case of non-surviving participants, study centres were asked to give a likely cause of death. Hypothermia was associated with an excess number of deaths as a consequence of sepsis/ARDS/MOF. In the TH group, significantly more participants who died had increased organ dysfunction scores, but this study cannot prove causality. With an absence of any difference in comorbidities or cointerventions between groups, the differences in the cause of death and the incidence of non-neurological organ dysfunction among those who died point to profound systemic consequences of hypothermia in this population of participants.

The harmful systemic effects of inflammation, linking sepsis, lung injury and MOF as a pathogenic consequence of TH, might explain the greater requirement for cardiovascular support, the evidence of tissue hypoperfusion and greater incidence of organ dysfunction associated with TH deaths.

One trigger for inflammation and organ dysfunction with TH may stem from a reduction in oxygen availability at a cellular level. Hypothermia causes a decrease in the tension/partial pressure of dissolved gases in the blood because of their increased solubility. This is accompanied by an increase in blood pH. A reduction in PaCO_2 , pH and temperature causes a leftward shift in the oxyhaemoglobin dissociation curve (OHDC),¹³² making less oxygen available in tissues.¹³³

The alpha-stat blood gas management is a simple and reliable method used by the 33 centres that participated in the Eurotherm3235 Trial and also in other hypothermia trials, such as the NABISH II and TTM trials.^{108,134} It may be beneficial for participants with cerebrovascular disease or derangements of cerebral autoregulation. Murkin *et al.*¹³⁵ compared pH-stat and alpha-stat strategies and found that flow–metabolism coupling was preserved using alpha-stat. Conversely, Kiziltan *et al.*¹³⁶ found that the pH-stat management might suppress the cerebral metabolic rate of oxygen more than the alpha-stat. In addition, under pH-stat conditions, there is a decrease in haemoglobin affinity for oxygen compared with alpha-stat, which could provide more dissolved oxygen for tissues. Similarly, Sakamoto *et al.*¹³⁷ showed that the pH-stat management increases cerebral oxygenation through improved oxygen delivery compared with alpha-stat. Higher oxyhaemoglobin and lower deoxyhaemoglobin levels were identified on cerebral near-infrared spectroscopy. The optimal strategy for blood gas management in TH remains uncertain and was not addressed in the majority of laboratory studies we reviewed prior to studying this intervention.

In order to maintain cerebral autoregulation, the alpha-stat acid–base management for arterial blood gases analysis was used in this trial and will have exacerbated tissue oxygen delivery. For example, a cooled participant with an alpha-stat PaCO_2 of 40 mmHg (measured at 37 °C) will have a substantially lower PaCO_2 at actual tissue temperature (32–35 °C) and a higher pH. A reduction in tissue oxygen delivery will be compounded by the reduction in cerebral blood flow (due to autoregulation) as PaCO_2 decreases. The net result of this is a failure in oxygen delivery, tissue acidosis and a pro-inflammatory state. This relative tissue hypoxia will affect not only the brain, but every organ system. Hypothermia creates a new and heterogeneous blood flow distribution, with areas of hypoxia and lactic acid generation. Such systematic effects might explain the greater use of vasopressors and inotropes in the TH group and the increased use of steroids. This would also be in keeping with the small but significant increase in the average daily lactate concentration and the greater prevalence of metabolic acidosis in the TH group.

During rewarming, there is a rightward shift of the OHDC, which facilitates oxygen dissociation. Morray *et al.*¹³⁸ documented an increase in $\dot{V}O_2$ during rewarming and found that oxygen delivery failed to keep pace with this $\dot{V}O_2$. Prolonged hypothermia may reduce blood flow through arterioles because of local factors such as a decrease in oxygen requirement, vasoconstriction and a reduction in plasma volume. Heterogeneous areas of blood flow distribution, tissue oxygen debt, an increment in lactate concentration and a metabolic acidosis will result. During rewarming, lactate re-enters normal oxidative pathways, consuming oxygen during this process. With a return to normothermia, free radical oxidation resumes, leading to non-respiratory utilisation of oxygen and an increase in $\dot{V}O_2$.

To detect and prevent brain hypoxia, the use of brain tissue oxygen tension (P_{btO_2}) monitoring as part of a multimodality array of advanced cerebral monitoring is becoming increasingly common. Frequent and long duration of cerebral hypoxaemic episodes in trauma patients have been repeatedly found to be significantly associated with poor outcome.¹³⁹ By manipulating CPP and ICP, and optimising PaO_2 , $PaCO_2$ and blood haemoglobin concentration, it is possible to improve P_{btO_2} .¹¹²

In a small, single-centre, retrospective analysis of the first 17 participants enrolled in the Eurotherm3235 Trial, Flynn *et al.*¹⁴⁰ found that there was a significant decline in mean P_{btO_2} from 30.2 mmHg to 22.4 mmHg in the TH group, from induction to stable hypothermia. In five out of the nine TH participants, P_{btO_2} fell below the target value of 20 mmHg but was unaffected by cooling in the remainder of the TH group. This raises the possibility that the response to cooling could be heterogeneous. For some patients, TH might reduce oxygen delivery to the brain to a greater degree than the reduction in metabolic oxygen consumption that occurs with cooling. However, this effect is not universal. A greater understanding of why cooling might be better tolerated in some patients, how to mitigate the effects of cooling on oxygen supply and of the use of cooling to a target P_{btO_2} might improve the results of TH in this group of patients.

Although anaemia has also been associated with a decrease in P_{btO_2} following TBI, this exploratory analysis found no statistically significant difference in the average daily mean of haemoglobin and haematocrit levels in the two groups.¹⁴¹

We found no evidence of a significant imbalance in propofol use or infusion rate between the treatment allocations.¹⁴² Similarly, there was no significant difference in propofol dose after adjustment for age, post resuscitation GCS motor component, time from injury and pupil reactivity. Furthermore, there were no statistically significant differences between the two groups in the number of participants receiving potentially toxic (> 5 mg/kg/hour) rates of propofol in the first 48 hours.^{143,144}

These comparisons, however, do not consider the effect of cooling on the metabolism of propofol, which, by slowing clearance, could potentially promote toxicity. Leslie *et al.*¹⁴⁵ demonstrated an approximate 28% increase in the serum concentration of propofol in six patients cooled to 34 °C. Moreover, the study showed a decrease in the hepatic blood flow by 10% with cooling. Bjelland *et al.*¹⁴⁶ showed that propofol clearance was significantly lower during hypothermia than normothermia (median 2046 vs. 2665 ml/minute; $p < 0.035$) in 14 patients treated with TH following cardiac arrest.

That said, the average daily liver and kidney function tests did not differ between the groups and there were no differences in the need for RRT, evidence of rhabdomyolysis or cardiac damage by treatment allocation. These findings would argue against the effect of propofol-related infusion syndrome (PRIS) in the TH group. The greater use of vasopressors and inotropes in the TH group may reflect a response to cardiovascular compromise because of an inflammatory state rather than the cardiotoxic effects of PRIS.

Hypothermia can also affect the clearance of other drugs, including neuromuscular blocking agents.¹⁴⁷ In this analysis, we found that atracurium was used more often in the TH group, possibly in an effort to manage shivering, than in the control group. However, the median hourly infusion rate was significantly lower with TH than with standard treatment; this could be explained by the reduction in the clearance of atracurium, which is temperature dependent by Hofmann degradation.

Decompressive craniectomy is performed in many neurotrauma centres worldwide. Over the course of our study, two important trials^{148,149} were either published or nearing completion. These trials found that decompressive craniectomy was associated with either a worse GOSE score at 6 months or greater survival but no improvement in the proportion of patients with good recovery. In our study, the number of participants undergoing decompressive craniectomy before and after randomisation was similar in the two groups. The use of hemicraniectomy and bifrontal craniectomy did not vary by CT appearance in either the TH group or the control group, nor was there a difference in Marshall scores by treatment allocation for either decompressive technique.

The literature at the time of the Eurotherm3235 Trial did not recommend the use of steroids to improve outcomes or reduce ICP.⁸⁶ The large, multicentre CRASH trial¹⁵⁰ found worse outcomes at 6 months and a higher mortality within 2 weeks in patients treated with methylprednisolone (Consilient Health Ltd, Surrey, UK). The mechanism and cause of the increase in death rate were not clear. The data from the exploratory analysis in this report revealed that the number of participants receiving steroids was significantly greater in the TH group than in the control group. However, when used, the steroids were of a relatively low dose compared with those used in the CRASH trial, and more in keeping with an adrenocortical replacement dose, such as what might be used in severe sepsis.

The Eurotherm3235 Trial was stopped early because of futility and safety concerns. The main trial was designed to be pragmatic, namely focused on functional outcome rather than on detailed mechanistic pathways. The fact that the study was stopped earlier than intended may introduce the risk of bias, reducing the validity of the results.¹⁵¹ For this exploratory analysis, the Eurotherm3235 Trial team successfully collected data on 74% of the ITT population, and received 286 anonymised CRFs out of 387 by post or e-mail to the Eurotherm3235 Trial office by the deadline of 31 July 2016. The main reasons that we received a smaller number of data than initially hoped for were that, among the 33 centres that took part in the main trial, three sites were closed, three did not have the capacity for collecting data and eight were inactive.

Chapter 7 Conclusions

Hypothermia with alpha-stat blood gas management is associated with important systemic effects, manifested as an inflammatory condition similar to sepsis/ARDS/MOF. This condition is associated with increased mortality and poorer outcomes after TBI.

Impact of patient and public involvement, challenges of patient and public involvement and lessons learnt

The Eurothern3235 Trial recruited patient populations that were very challenging for two main reasons:

1. Patients were incapacitated because they were sedated and connected to a ventilator at the time of recruitment to the trial.
2. There is a high probability of a poor outcome following TBI; therefore, patients who have survived their injury generally have many problems, either cognitively or physically, that impair their ability to contribute to the design of a research trial.

This made patient involvement in the design and structure of the trial very difficult. For these reasons, it was not possible to have a patient representative as part of the protocol design group; however, we did involve a group of patients who had suffered a TBI and their relatives in the design and writing of the patient and relative documentation. The patients and relatives involved were suggested to us by the Edinburgh Headway Group, and time since suffering the TBI ranged from 2 to 25 years.

The trial manager (H Louise Sinclair) visited the Edinburgh Headway Group on a day, arranged by the group, when the suggested patients and relatives would attend. The patients were given the draft patient consent forms and patient information sheets to read, and the relatives were given the draft patient and relative consent forms and information sheets to comment on. The patients were interviewed individually by H Louise Sinclair and any comments were documented. The main comment from patients was that the forms were too complicated; they struggled to understand some of the wording and could not read the forms because of the font (Times New Roman) and the small font size that was used.

The relatives were also interviewed individually and their comments were documented. The main concerns were:

- The length of the information sheets for both patients and relatives.
- The formal layout of the information sheets – A4 size double-sided documents.
- The complexity of the wording used for patients – we needed to use much more basic language (approximately at the level of an 8-year-old).
- The complexity of the wording used for relatives. The concerns were that, at the time of reading the documents and consent forms, relatives would be in a state of shock so would be unable to process a lot of information.

The consent documents were then amended, taking into account all of the comments and concerns raised. We could not reword the consent forms because they were written in accordance with the NRES guidelines for wording consent forms and information sheets;¹⁵² however, we were able to change the layout of these documents. In doing so, we changed the font used and increased the font size of the consent forms, and changed the layout of the information sheets to an A5-sized booklet using basic language, an informal, larger font and the use of colour text boxes. H Louise Sinclair then met with the same cohort and the forms were approved by the group.

We also appointed a patient's relative as a lay member of the Trial Steering Committee. She was recommended by Edinburgh Headway Group and attended the steering committee meetings in person. She did, however, find being a member of the committee difficult at times because she is her husband's main carer and could not leave him at home alone for the duration of the meeting. She therefore had to arrange for carers to be with him while she attended the meetings. She also found the role upsetting at times because she described how it brought back memories of her husband's brain injury, his stay in intensive care and subsequent difficult recovery with the adaptations she has had to make to their lives.

Conclusions

In patients with TBI, TH plus standard care successfully reduced ICP. This intervention, however, did not improve functional recovery as compared with standard care alone.

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Contributions of authors

Peter JD Andrews was responsible for the conception of the work and the design of the database for the acquisition, analysis or interpretation of data, drafting the work and revising it for important intellectual content and giving final approval of the published version.

H Louise Sinclair made substantial contributions to the design of the work, and the acquisition, analysis and interpretation of data. She was responsible for drafting the work, revising it critically for important intellectual content and giving final approval of the published version.

Aryelly Rodríguez was responsible for the analysis of data, drafting the work or revising it critically for important intellectual content and giving final approval of the published version.

Bridget Harris made substantial contributions to the design of the work, and the acquisition, analysis and interpretation of data. She was responsible for drafting the work or revising it critically for important intellectual content.

Jonathan Rhodes made substantial contributions to the analysis and interpretation of data (author of *Chapter 6*) and gave final approval of the published version.

Hannah Watson made substantial contributions to the analysis and interpretation of data (author of *Chapter 4*) and gave final approval of the published version.

Gordon Murray created the trial design and was the author of the statistical analysis plan. He was responsible for drafting the work or revising it critically for important intellectual content.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/data-citation>.

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Appendix 1 Induction and maintenance of therapeutic hypothermia

BOX 1 Induction and maintenance of hypothermia guideline

Patient randomised to hypothermia

Continue stage 1 and 2 therapy as indicated throughout the hypothermia/rewarming interventions.

Prior to induction of hypothermia

- Opiate and propofol (suggested dosage of 10 µg/kg/minute) or midazolam infusions.
- Paracetamol (1 g/6 hours oral/rectal/intravenously).
- Ensure that extremities are covered.
- Ensure that the maintenance method of hypothermia is in place and ready for use.
- Core temperature monitoring in place – bladder, oesophageal, pulmonary artery catheter or rectum.
- Assess baseline laboratory values as appropriate.

Induction of hypothermia

- Infuse 20–30 ml/kg of refrigerated 0.9% saline intravenously within 30 minutes.
- Closely monitor all vital signs during the induction phase of hypothermia.
- Observe continuously for obvious signs of shivering.
- Assess for signs of shivering using the shivering assessment tool every 30 minutes during the first 2 hours and hourly thereafter, and if there is any indication of shivering between these times.

Maintenance of hypothermia

- Maintain hypothermia for > 48 hours.
- Maintain ICP of ≤ 20 mmHg by adjusting temperature (32–35 °C) (i.e. higher ICP may require a lower temperature).
- Assess laboratory values as appropriate during hypothermia therapy.
- Observe continuously for obvious signs of shivering.
- Assess for signs of shivering using the shivering assessment tool every 30 minutes during the first 2 hours and hourly thereafter, and if there is any indication of shivering between these times.
- Please note that all participants should be closely monitored and their care assessed to avoid any side effects of induced hypothermia therapy:
 - hypovolaemia
 - respiratory and metabolic acidosis
 - hypokalaemia
 - relative drug overdose
 - hypotension
 - coagulopathy.

BOX 2 Rewarming guideline**Rewarming phase**

There is no maximum duration of hypothermia; however, rewarming should first be considered 48 hours from induction of hypothermia only if ICP is ≤ 20 mmHg.

Rewarming rate: 1 °C/4 hours (0.25 °C per hour) until core temperature is ≥ 36 °C.

Assess laboratory values as appropriate.

All patients should be closely monitored and their care assessed to avoid any side effects:

- hypotension
- hypovolaemia
- hyperkalaemia
- arrhythmias.

Pause rewarming if ICP is > 20 mmHg and if necessary recool to maintain ICP of ≤ 20 mmHg.

Consider stage 3 options if necessary:

- barbiturate infusion
- decompressive craniectomy.

Appendix 2 Detection and treatment of shivering

BOX 3 Shivering detection guideline

Prior to induction of hypothermia

- Opiate and propofol or midazolam infusions.
- Paracetamol (1 g/6 hours enterally/intravenously).
- Ensure that extremities are covered.

Induction of hypothermia (cold saline with/without cooling method or device)

- Observe continuously for obvious signs of shivering.
- Assess for signs of shivering using the shivering assessment tool every 15 minutes until target temperature achieved.

Maintenance of hypothermia (cooling method or device)

- Observe continuously for obvious signs of shivering.
- Assess for signs of shivering using the shivering assessment tool every 30 minutes during the first 2 hours and hourly thereafter, and if there is any indication of shivering between these times.

BOX 4 Shivering detection guideline: shivering assessment tool

Observe ECG and/or BIS trace continuously for artefact.

Formal assessment.

Observe patient for 2 minutes, during which time visually inspect and palpate jaw, neck, chest, arms and legs.

Score shivering as follows:

- 0 = no shivering
- 1 = mild: shivering localised to jaw, neck and/or chest only
- 2 = moderate: shivering involves gross movement of arms or legs, in addition to neck, chest and two extremities
- 3 = severe: shivering involves gross movements of the trunk and arms and legs.

If the patient scores ≥ 1 using this scale, please refer to the *Prevention of Shivering Guideline* overleaf.

BIS, Bispectral Index; ECG, electrocardiogram.

Based on recommendations in Badjatia *et al.*⁹⁵

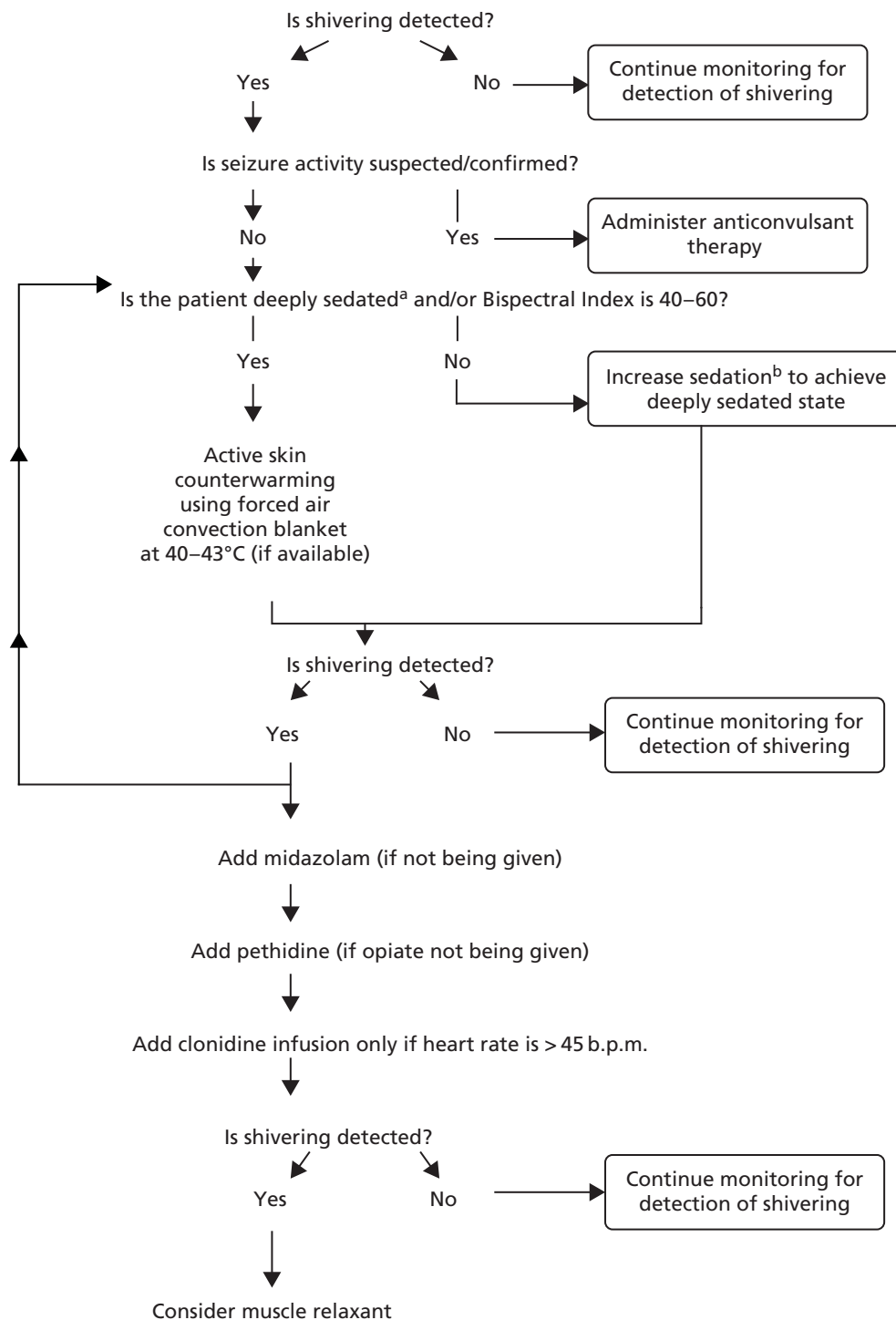


FIGURE 18 Shivering treatment guideline. a, Definition of 'deeply sedated' – no response to voice, but movement or eye opening to physical stimulation. b, Increase in propofol dose every 10 minutes until deeply sedated state is achieved and/or Bispectral Index. b.p.m., beats per minute.

Appendix 3 Data Safety Monitoring Committee charter

DATA MONITORING COMMITTEE (DMC) CHARTER FOR THE EUROTHER3235 TRIAL
VERSION 1.0 27/04/2009

EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE STUDY OF THERAPEUTIC
HYPOTHERMIA (32-35°C) AFTER TRAUMATIC BRAIN INJURY

VERSION 1.1 25.05.2009

1. INTRODUCTION

The trial is funded by the European Society of Intensive Care Medicine. REC approval has been gained in Scotland and England. CAS reference 09/MRE00/34 (Scotland AWI Study) and 09/H1302/44 (England and Wales ALC study).

The trial is registered on the European registry of trials (www.controlledtrials.com, ISRCTN ISRCTN34555414)

1.1. Trial Objectives

The EUROTHERM3235 Trial is an international trial in neurological intensive care that will confirm or refute the research question, does therapeutic hypothermia (32-35°C) reduce morbidity and mortality rates at 6 months after TBI assessed by the extended Glasgow Outcome Scale questionnaire?

Other questions that will be answered include:

Does therapeutic hypothermia (32-35°C) reduce intra cranial hypertension? And is therapeutic hypothermia a cost effective treatment to improve outcome after TBI?

1.2. Scope

The purpose of this document is to describe the roles and responsibilities of the independent DMC for EUROTHERM, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other committees

2. ROLES AND RESPONSIBILITIES

2.1. Aims

To protect and serve EUROTHERM participants, in particular with regard to safety and to assist and advise Principal Investigators so as to protect the validity and credibility of the trial. To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial.

2.2. Terms of reference

The DMC should receive and review the progress and accruing data of the EURO THERM trial and provide advice on the conduct of the trial to the Trial Steering Committee. The DMC should inform the Chair of the steering committee if, in their view the results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that on balance one trial arm is clearly indicated or contraindicated for all participants or a particular category of participants, and there was a reasonable expectation that this new evidence would materially influence patient management.

2.3. Specific roles of DMC

Interim review of the trial's progress including updated figures on recruitment, data quality, and main outcomes and safety data. This review would include, but not be restricted to, the following:

- assess data quality, including completeness (and by so doing encourage collection of high quality data)
- monitor recruitment figures and losses to follow-up
- monitor compliance with the protocol by participants and investigators
- monitor evidence for treatment differences in the main efficacy outcome measures
- monitor evidence for treatment harm (e.g. toxicity data, SAEs, deaths)
- decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups
- suggest additional data analyses
- monitor planned sample size assumptions
- monitor continuing appropriateness of patient information
- monitor compliance with previous DMC recommendations
- consider the ethical implications of any recommendations made by the DMC
- assess the impact and relevance of external evidence

3. BEFORE OR EARLY IN THE TRIAL

3.1. DMC input into the protocol

All potential DMC members should have sight of the protocol before agreeing to join the committee. Before recruitment began the trial had undergone review by the ESICM and a REC. Therefore, if a potential DMC member has major reservations about the trial (e.g. the protocol or the logistics) they should report these to the Chief Investigator and may decide not to accept the invitation to join. DMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.

3.2. Timing of 1st DMC meeting

The 1st meeting of the DMC has been scheduled for early in the course of the trial, to discuss the protocol, the trial, any analysis plan, future meetings, and to have the

opportunity to clarify any aspects with the principal investigators, and to discuss the format of reports to the DMC from the Trial Office (in the Edinburgh Clinical Trials Unit, University of Edinburgh). Subsequent meetings of the DMC will, where possible, be timed to precede a trial Steering Committee meeting by a few weeks.

3.3.DMC member's contracts

Members of a DMC will have indemnity cover from the Sponsor for their work on the DMC.

4. COMPOSITION

4.1.DMC Membership

The DMC members are independent of the trial (that is, they are not involved with the EUROTHERM trial in any other way or have some competing interest that could impact on the EUROTHERM trial). Any competing interests, both real and potential, should be declared. A short competing interest form should be completed and returned by the DMC members to the Chief Investigator, Peter Andrews, at Western General Infirmary Edinburgh. The members of the DMC for the EUROTHERM trial are:

- Professor Peter M. Suter, Président ASSM/SAMW, Centre Médical Universitaire, Université de Genève, Rue Michel-Servet 1, CH-1211 Genève, Switzerland
- Professor Ian Ford, Professor of Statistics, Robertson Centre for Biostatistics, Glasgow
- Professor Peter Sandercock, University of Edinburgh, Edinburgh

4.2.The responsibilities of the DMC statistician

Professor Ian Ford will act as the DMC statistician, guiding the DMC on the statistical interpretation of the reports they receive. Professor Ford will liaise with the trial statistician on the specification of the statistical analyses and reports, which will be produced for him.

4.3.The responsibilities of the trial statistician

The independent statistician (located in ECTU Office) in conjunction with ECTU Senior Trial Coordinator (Bridget Colam) will oversee production of reports to the DMC and if appropriate the independent statistician will participate in DMC meetings, guiding the DMC through the report, participating in DMC discussions and, on some occasions, taking notes.

4.4.The responsibilities of the Trial Office

The Trial Office team comprises:

- Clinical Coordinator [Jonathan Rhodes]
- Trial Manager [Louise Sinclair]
- Data Manager [TBA]
- Senior Trial Manager [Bridget Colam]
- Experienced Trialist [Stuart Ralston]
- Trial Statistician [Gordon Murray]
- Independent Statistician [TBA]

With the exception of the independent statistician, these Trial Office staff will usually only contribute to the production of the non-confidential sections of DMC reports.

4.5. The responsibilities of the Chief Investigator and other members of the EUROTHERM Trial Steering Committee

The Chief Investigator (Peter Andrews), may be asked, and should be available, to attend open sessions of the DMC meeting. Other EUROTHERM Steering Committee members will not usually be expected to attend but can attend open sessions when necessary.

5. RELATIONSHIPS

5.1. Relationships between study teams

The study is guided by a Trial Steering Committee that meets approximately annually. The TSC has an independent chair, additional independent members, the grant holders and principal investigators, and members of the Trials Office. The day to day running of the trial is overseen by the Project Management Group, who meet weekly at the Trial Office and are joined by the Chief Investigator. The Trial Management Team in addition meet face to face approximately every 6-8 weeks.

5.2. Advisory role of DMC

As is customary, the EUROTHERM DMC will not make decisions about the trial, but rather make recommendations to the EUROTHERM Steering Committee from the DMC Chair to the Chief Investigator.

5.3. DMC payments

EUROTHERM DMC members will be reimbursed for travel and accommodation. No other payments or rewards are anticipated.

5.4. DMC members competing interests

Competing interests should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility. (See Annex 1)

DMC members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.

6. ORGANISATION OF DMC MEETINGS

6.1. Frequency of DMC meetings

It is recommended that the DMC meet at least yearly. If possible the DMC meetings should be arranged to take place just prior to planned meeting of the Trial Steering Committee, so that the DMC report can be considered by the Trial Steering Committee in a timely fashion.

6.2.DMC meetings location and style

It is expected that all the meetings will be face-to-face with teleconferencing if required.

6.3.DMC meetings format

- Open session: Introduction and any “open” parts of the report
- Closed session: DMC discussion of “closed” parts of the report

And, if necessary;

- Further open session: Discussion with other attendees on any matters arising from the previous session(s).
- Further closed session: extra closed session

7. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION

7.1.Intended content for open sessions

Accumulating information relating to recruitment and data quality (e.g. data return rates, treatment compliance) will be presented. SAE details based on pooled data will be presented and total numbers of events for the primary outcome measure and other outcome measures may be presented, at the discretion of the DMC.

7.2.Intended content for closed sessions

In addition to all the material available in the open session, the closed session material will include efficacy and safety data by treatment group.

7.3.DMC blinding

DMC will not be blind to treatment allocation. However the randomised groups will be labelled A and B. The identity of A and B will be supplied under separate cover, not in the report.

7.4.Access to accumulating data and interim analysis

No study personnel, with the exception of the independent statistician and his delegates (for example, a junior statistician to perform the analyses under the independent statistician’s supervision, or a clerical assistant to format the reports) will be unblinded to any study results during the conduct of the study. DMC members do not have the right to share confidential information with anyone outside the DMC, including the Chief Investigator.

7.5.Responsibility for identifying and circulating external evidence

The Chief Investigator (Peter Andrews) takes responsibility for the identification and circulation of external evidence (e.g. from other trials/ systematic reviews).

7.6.DMC communications

The DMC will report its recommendations in writing to the Trial Steering Committee. This will be copied to the trial statistician and if possible should be sent via the study data centre in time for consideration at a meeting of the Trial Steering Committee (See Annex 2)

7.7. Prior availability of DMC reports

The DMC will receive the independent statistician's report at least 1 week before a DMC meeting.

7.8. Destruction of confidential papers

The DMC members should destroy their reports after each meeting. If requested, fresh copies of previous reports will be circulated with the newest report before each meeting. The Trial Office will take responsibility for keeping all DMC study reports and minutes for inspection at study termination and for subsequent archiving.

8. DECISION MAKING

8.1. Possible DMC decisions/recommendations

Possible recommendations could include:-

- No action needed, trial continues as planned
- Early stopping due, for example, to clear benefit or harm of a treatment, futility, or external evidence
- Stopping recruitment within a subgroup
- Stopping the trial on the basis of futility of recruitment
- Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up
- Sanctioning and/or proposing protocol changes

8.2. Statistical guidelines for termination

The DMEC has the responsibility for deciding whether, while randomisation is in progress, the unblinded results (or the unblinded results for a particular subgroup), should be revealed to the TSC. The DMEC terms of reference state that they will do this if, and only if, two conditions are satisfied: (1) the blinded results provide proof beyond reasonable doubt that treatment is on balance either definitely harmful or definitely favourable for all, or for a particular category of patients, in terms of the major outcome; (2) the blinded results would, if revealed, be expected to substantially change the prescribing patterns of doctors who are already familiar with any other trial results that exist. Exact criteria for "proof beyond reasonable doubt" are not, and cannot be, specified by a purely mathematical stopping rule, but they are strongly influenced by such rules. DMEC members have expressed sympathy with the stopping rule proposed in Part I of the 1976 report to the MRC Leukaemia Committee, whereby an interim analysis of major endpoint would generally need to involve a difference between treatment and control of at least three standard errors to justify premature disclosure. An interim subgroup analysis would, of course, have to be even more extreme to justify disclosure. This rule has the advantage that the exact number and timing of interim analyses need not be pre-specified. In summary, the stopping rules as specified in the CRASH trial protocol (as successfully applied in other trials including the MRC International Stroke Trial, which randomised 19,436 acute stroke patients) require extreme differences to justify premature disclosure and involve an appropriate combination of mathematical stopping rules and scientific judgement.

8.3.DMC decision making methods

It is recommended that every effort should be made for the DMC to reach a unanimous decision. If the DMC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data. It is important that the implications (e.g. ethical, statistical, practical, and financial) for the trial be considered before any recommendation is made. The role of the Chair is to summarise discussions and encourage consensus; it may be best for the Chair to give their own opinion last.

8.4.DMC quorum for decision-making

Effort should be made for all members to attend. The trial coordinating office will ensure that a date is chosen to enable this. With only 3 members comprising the DMC, all members will need to be taking part (in person or by teleconference) for any major decision to be taken.

8.5.Non participation

If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DMC. If a member does not attend a third meeting, they should be replaced.

9. REPORTING

9.1.Communication of DMC recommendation

By letter to the Chief Investigator (Peter Andrews), within 3 weeks of the DMC meeting, with a copy of the letter to the Trial Office (ECTU, Edinburgh).

9.2.DMC Minutes

The DMC will keep an accurate minute of their discussions. Separate sections will be required for the open and closed sessions. The DMC Chair will sign off any minutes or notes. A sealed copy will be sent to the independent statistician at the Trial Office (ECTU, Edinburgh).

9.3.DMC and Steering Committee conflict resolution

If the DMC has serious problems or concerns with any Trial Steering Committee decisions a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DMC's concerns. Depending on the reason for the disagreement confidential data may have to be revealed to all those attending such a meeting. The meeting should be chaired by a senior member of the Trials Office or an external expert who is not directly involved with the trial

10.AFTER THE TRIAL

10.1. Publication of results

At the end of the trial there will be a meeting to allow the DMC to discuss the final data with the Chief Investigator and give advice about data interpretation. The Trial Steering Committee members are committed to publishing the results in a correct and timely manner, irrespective of the findings.

10.2. DMC information to be published

DMC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DMC meetings will be included in the body of this paper.

10.3. DMC role in publications

The DMC will be given the opportunity to read and comment on major publications before submission.

10.4. DMC confidentiality post study closedown

The DMC members may discuss details of their involvement after permission is agreed with the Trial Steering Committee.

Annex 1: Suggested EUROTHERM competing interests form Potential competing interests of Data Monitoring Committee members for EUROTHERM

The avoidance of any perception that members of a DMC may be biased in some fashion is important for the credibility of the decisions made by the DMC and for the integrity of the trial.

Possible competing interest should be disclosed via the trials office. In many cases simple disclosure up front should be sufficient. Otherwise, the DMC member should remove the conflict or stop participating in the DMC. Table 1 lists potential competing interests.

Table 1: Potential competing interests

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) in competing products
- Involvement in the publication

Please complete the following section and return to the trials office.

No, I have no competing interests to declare

Yes, I have competing interests to declare (please detail below)

Please provide details of

any competing interests:

Name: _____

Signed: _____ Date: _____

DATA MONITORING COMMITTEE (DMC) CHARTER FOR THE EUROTHER3235 TRIAL
VERSION 1.0 27/04/2009

DATA MONITORING COMMITTEE (DMC) CHARTER FOR THE EUROTHERM3235
TRIAL 9

Annex 2: Illustrative report from EUROTHERM DMC to
STEERING Committee where recommendation is to continue the
trial according to the protocol

[Insert date]

To: Chair of Trial Steering Committee

Dear [Chair of Trial Steering Committee]

The Data Monitoring Committee (DMC) for the EUROTHERM trial met on [meeting
date] to review its progress and interim accumulating data. [List members]
attended the meeting and reviewed the report.

The trial question remains important and, on the basis of the data reviewed at this
stage, we recommend continuation of the trial according to the current version of
the protocol [specify protocol version number and date] with no changes.

We shall next review the progress and data [provide approximate timing]

Yours sincerely,

[Name of meeting Chair]

Chair of Data Monitoring Committee

On behalf of the DMC (all members listed below)

DMC members:

(1) [Insert name and role]

(2) [Insert name and role]

(3) [Insert name and role]

Appendix 4 Systematic review protocol: PROSPERO international prospective register of systematic reviews

An update: systematic review for the treatment of traumatic brain injury using therapeutic hypothermia

Hannah Watson, Andrew Shepherd, Jonathan Rhodes, Peter Andrews, Margaret MacDougall

Citation

Hannah Watson, Andrew Shepherd, Jonathan Rhodes, Peter Andrews, Margaret MacDougall. An update: systematic review for the treatment of traumatic brain injury using therapeutic hypothermia. PROSPERO

2016:CRD42016036137 Available from

http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42016036137

Review question(s)

The purpose of this review is to update the evidence base for the use of therapeutic hypothermia in adult patients with traumatic brain injury following the recent publication of two randomised controlled trials.

Searches

The following electronic resources will be searched:

- Cochrane Central Register of Controlled Trials (CENTRAL)
- EMBASE
- MEDLINE
- PubMed

Other notes:

- Only foreign articles published in the English language will be included.
- The electronic search will span from January 2011 to March 2016 and so will be complementary to the current evidence base
(<http://www.ncbi.nlm.nih.gov/pubmed/?term=crossley+andrews+traumatic+brain+injury>).

Types of study to be included

This review will only include randomised clinical trials.

Condition or domain being studied

The condition being studied is adult traumatic brain injury sustained following acute closed head trauma. Therapeutic hypothermia is the intervention of interest.

For the purpose of this review therapeutic hypothermia is defined as any intervention with the intention of reducing core body temperature to below the physiological norm (36 degrees Celsius).

Patient outcomes at follow-up will be assessed according to mortality and morbidity data. There will be a particular emphasis on outcomes recorded on a scale, for example, the Glasgow Outcome Scale or Ranchos Los Amigos Scale.

Participants/ population

Inclusion Criteria:

- Randomisation.
- Control group.
- Use of therapeutic hypothermia
- Adult patients, taken as the legal age of consent in the country of trial origin.
- Closed head injury.

Exclusion Criteria:

- No control group.
- Neonatal or paediatric patients.
- Open head injuries, including gunshot wounds.

Only articles meeting all inclusion criteria and no exclusion criteria will be included.

Intervention(s), exposure(s)

The intervention of interest is therapeutic hypothermia.

Inclusion:

- Any method of temperature reduction.

Exclusion:

- No article will be excluded on the basis of their cooling technique.

For all articles the method of cooling will be detailed during data extraction. Other intervention factors that the authors may feel relevant, e.g. use of barbiturates, will also be noted during data extraction.

Comparator(s)/ control

This review will only include studies that detail a normothermic or no temperature reduction control group.

Context

Adult patients with moderate (Glasgow Coma Scale (GCS) 9-12) and severe (GCS ≤ 8) acute traumatic brain injury and admitted to an intensive care unit.

Outcome(s)**Primary outcomes**

The primary outcomes that will be assessed are mortality and morbidity, including, new pneumonia. Morbidity will

be assessed using the Glasgow Outcome Scale Extended or Glasgow Outcome Scale at six months.

Death or discharge Modified Oxford handicap scale will be used at 28 days.

Secondary outcomes

The following will be investigated as secondary hypotheses:

- a) Duration of cooling over 48 hours confers improved outcomes compared to less than 48 hours duration.
- b) The re-warming of patients at a rate of greater than 1 degree Celsius every four hours increases the risk of poor outcome.
- c) Those patients cooled to below 35 degrees Celsius will have a better outcome at follow-up compared to more moderate cooling of 35-36 degrees Celsius.
- d) An increasing time between injury onset and temperature reduction is associated with a poorer outcome.
- e) Hypothermia intervention is not more effective when the control group is managed to normothermia.

Poor outcome at six months with the GOSE dichotomised 1-5 and 6-8.

Data extraction, (selection and coding)

The PRISMA statement will be followed at all stages.

There are four co-authors that will be involved with abstract screening, full-text review and data extraction.

A minimum of two independent reviewers will assess each title/abstract found by the searches against the defined inclusion and exclusion criteria. Any discrepancies will be resolved by one of the senior co-authors. Reasons for exclusion will be noted.

All included abstracts will then undergo full-text review and data extraction by two of the co-authors. As before, any discrepancies will be resolved by one of the senior co-authors.

Risk of bias (quality) assessment

The following proforma will be used to assess the risk of bias:

A) Allocation Concealment

The randomisation methodology will be defined as adequate, inadequate or unclear. Definitions:

- i. Adequate - Neither the investigator nor participant knows or could influence the intervention group prior to participant enrollment.
- ii. Inadequate - Any indication that there was influence over the intervention group or use of a poor randomization technique employed, for example, unsealed envelopes etc.
- iii. Unclear - No information on randomisation methodology.

B) Blinding

Blinding of investigators: Yes/No/Not stated

Blinding of participants: Yes/No/Not stated

Blinding of outcome assessor: Yes/No/Not stated

Blinding of data analysis: Yes/No/Not stated

C) Intention-to-Treat Analysis (Yes/No/Not stated)

Yes - 1. Specifically reported by the authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment; 2. Not stated, but confirmed on study assessment.

No - 1. Not reported and lack of intention-to-treat analysis confirmed on study assessment*; 2. Stated but not confirmed upon study assessment.

*(For example, patients who were randomised but not included in the analysis because they did not receive the study intervention, they withdrew from the study, or were not included because of protocol violation).

D) Completeness of follow-up will be documented as the percentage of patients excluded or lost to follow-up.

The quality of individual studies may be assessed using the Downs and Black Quality Checklist (1998).

Strategy for data synthesis

The data used will be aggregate with both quantitative and qualitative analysis.

With respect to temperature data the difference in means will be calculated with 95% confidence intervals. If the quality of trials allows then a meta-analysis of weighted mean difference will be calculated. A statistical significance level of 0.05 will be used for all hypothesis testing. Statistical heterogeneity will be tested for by means of the Q test and I-squared index. Depending on the outcomes forthcoming from applying these procedures, relative risk and 95% confidence intervals for all-cause mortality an improved neurological outcome will be calculated using a random-effects model or fixed effect model. Subsequent models may be applied should the data be suitable for meta-analysis. When appropriate, sensitivity analyses as based on study quality (risk of bias) will be conducted.

Analysis of subgroups or subsets

Specific subgroups that may be analysed are:

- Earlier versus more recent trial data to determine whether there is a change of effect over time.
- Controlled normothermia or no temperature control.
- Trials that used propofol sedation.

Dissemination plans

Peer review publication; local, national and possibly international presentation; uploading to Eurotherm3235Trial

website; inclusion in HTA monograph on HTA project 11/01/30 Eurotherm3235.

Contact details for further information

Hannah Watson

Peter JD Andrews

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Organisational affiliation of the review

NHS Lothian and the University of Edinburgh

<http://www.nhsllothian.scot.nhs.uk/Pages/default.aspx>

Review team

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Details of any existing review of the same topic by the same authors

Crossley S, Reid J, Mc Latchie R, Hayton J, Clark C, MacDougall M, Andrews PJ. A systematic review of therapeutic hypothermia for adult patients following traumatic brain injury. *Crit Care*. 2014 Apr 17;18(2):R75. doi: 10.1186/cc13835.

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Conflicts of interest

None known

Language

English

Country

Scotland

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Subject indexing assigned by CRD

Subject index terms

Brain Injuries; Humans; Hypothermia, Induced

Stage of review Ongoing

Date of registration in PROSPERO

27 October 2016

Date of publication of this revision

27 October 2016

| Stage of review at time of this submission | Started | Completed |
|---|----------------|------------------|
| Preliminary searches | Yes | No |
| Piloting of the study selection process | Yes | No |
| Formal screening of search results against eligibility criteria | Yes | No |
| Data extraction | No | No |
| Risk of bias (quality) assessment | No | No |
| Data analysis | No | No |

Search strategies:

Thank you to Ms Shiela Fiskien of the University of Edinburgh Library for her help in both developing our search strategies and in accessing the databases that were used.

The search terms that have been used are complimentary to those from Crossley 2014.

A full alphabetical list of our search terms may be found below our individual strategies.

Pubmed search strategy:

(((((randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR randomly[Title/Abstract] OR random order[Title/Abstract] OR random sequence[Title/Abstract] OR random allocation[Title/Abstract] OR randomly allocated[Title/Abstract] OR at random[Title/Abstract])) OR randomized controlled trial[MeSH Terms]) NOT ((models, animal[MeSH Terms] OR animals[MeSH Terms] OR animal experimentation[MeSH Terms] OR disease models, animal[MeSH Terms] OR animals, laboratory[MeSH Terms]) NOT (humans[MeSH Terms]))) AND Humans[Mesh] AND (((((hypotherm*[Title/Abstract] OR normotherm*[Title/Abstract] OR cool*[Title/Abstract] OR cold*[Title/Abstract] OR temperature*[Title/Abstract] OR cryother*[Title/Abstract] OR cryogen*[Title/Abstract] OR cryotreat*[Title/Abstract])) OR (((((refrigeration*[Title/Abstract] OR cryo*[Title/Abstract]) AND anaesthes*[Title/Abstract])) OR ((cool*[Title/Abstract] OR cold*[Title/Abstract]) AND (therap*[Title/Abstract] OR device*[Title/Abstract] OR equipment*[Title/Abstract])) OR (temperature[Title/Abstract] AND (reduc*[Title/Abstract] OR low*[Title/Abstract])) OR ((cool*[Title/Abstract] OR cold*[Title/Abstract]) AND (blanket*[Title/Abstract] OR neck collar*[Title/Abstract] OR helmet*[Title/Abstract] OR hood*[Title/Abstract])) OR (intravenous[Title/Abstract] AND (cold*[Title/Abstract] OR cool*[Title/Abstract]) AND (fluid*[Title/Abstract] OR catheter*[Title/Abstract])))) OR (((induced hypothermia[MeSH Terms]) OR cryotherapy[MeSH Terms]) OR hypothermia[MeSH Terms]) AND (((((((((((Craniocerebral Trauma[MeSH Terms]) OR Brain Edema[MeSH Terms]) OR Glasgow Coma Scale[MeSH Terms]) OR glasgow outcome scale[MeSH Terms]) OR Unconsciousness[MeSH Terms]) OR Cerebrovascular Trauma[MeSH Terms]) OR intracranial hypertension[MeSH Terms]) OR (((head[Title/Abstract] OR cranial[Title/Abstract] OR cerebral[Title/Abstract] OR capitis[Title/Abstract] OR brain[Title/Abstract] OR forebrain*[Title/Abstract] OR skull*[Title/Abstract] OR Hemisphere*[Title/Abstract] OR intra-cran*[Title/Abstract] OR inter-cran*[Title/Abstract]) AND (injur*[Title/Abstract] OR trauma[Title/Abstract] OR damag*[Title/Abstract] OR wound*[Title/Abstract] OR fracture*[Title/Abstract] OR contusion*[Title/Abstract] OR concuss*[Title/Abstract] OR pressure*[Title/Abstract])))) OR (((head[Title/Abstract] OR cranial[Title/Abstract] OR cerebral[Title/Abstract] OR capitis[Title/Abstract] OR brain[Title/Abstract] OR forebrain*[Title/Abstract] OR skull*[Title/Abstract] OR hemisphere*[Title/Abstract] OR intra-cran*[Title/Abstract] OR inter-cran*[Title/Abstract] OR tentori*[Title/Abstract]) AND (haematoma*[Title/Abstract] OR hematoma*[Title/Abstract] OR haemorrhag*[Title/Abstract] OR hemorrhag*[Title/Abstract] OR Bleed*[Title/Abstract] OR hernia*[Title/Abstract] OR oedema*[Title/Abstract] OR edema*[Title/Abstract] OR swell*[Title/Abstract])))) OR ((glasgow[Title/Abstract] AND (scale[Title/Abstract] OR score[Title/Abstract]) AND (outcome[Title/Abstract] OR coma[Title/Abstract])) OR ranchos Los amigos[Title/Abstract] OR diffuse axonal injur*[Title/Abstract]) OR ((unconscious[Title/Abstract] OR coma*[Title/Abstract] OR concuss*[Title/Abstract] OR persistent vegetative state[Title/Abstract]) AND (injur*[Title/Abstract] OR trauma[Title/Abstract] OR damag*[Title/Abstract] OR wound*[Title/Abstract] OR fracture*[Title/Abstract]))))

Ovid Embase and Medline search strategy:

1. exp Craniocerebral Trauma/
2. Brain Edema/
3. glasgow coma scale/ or glasgow outcome scale/
4. exp Unconsciousness/
5. exp Cerebrovascular Trauma/
6. exp Intracranial Hypertension/
7. ((head or crani* or cerebr* or capitis or brain* or forebrain* or hemispher* or intrac-cran* or inter-cran*) adj3 (injur* or trauma* or damag* or wound* or fracture* or contusion* or concuss* or pressure*)).ti,ab.
8. ((head or cran* or cerebr* or capitis or tentori* or brain* or forebrain* or hemispher* or intra-cran* or inter-cran*) adj3 (haematoma* or hematoma* or hemorrhag* or haemorrhag* or bleed* or hernia* or oedema* or edema* or swell*)).ti,ab.
9. (Glasgow adj3 (coma or outcome*) adj3 (scale* or score*)).ti,ab.
10. "Rancho Los Amigos".ti,ab.
11. "diffuse axonal injur*".ti,ab.
12. ((unconscious* or coma* or concuss* or 'persistent vegetative state*') adj3 (injur* or trauma* or damag* or wound* or fracture*)).ti,ab.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp hypothermia, Induced/
15. exp Cryotherapy/
16. exp Profound Induced Hypothermia/
17. (hypotherm* or normother* or cool* or cold* or temperature* or cryother* or cryogen* or cryotreat*).ab,ti.
18. ((refrigeration* or cryo*) adj3 anaesthes*).ab,ti.
19. ((cool* or cold*) adj3 (therap* or device* or equipment*)).ab,ti.
20. (temperature adj3 (reduc* or low*)).ab,ti.
21. (intravenous adj3 (cold* or cool*) adj3 (fluid* or catheter*)).ab,ti.
22. ((cool* or cold*) adj3 (blanket* or neck collar* or helmet* or hood*)).ab,ti.
23. exp Hypothermia/
24. or/14-23
25. (randomised or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random or controlled clinical trial*).tw,hw.
26. clinical trial.pt.
27. randomized controlled trial.pt.
28. or/25-27
29. exp models, animal/
30. exp animals/
31. exp animal experimentation/
32. exp animals, laboratory/
33. or/29-32
34. Humans/
35. 33 not 34
36. 28 not 35
37. 13 and 24 and 36

Cochrane Central Register of Controlled Trials (Central) search strategy:

1. MeSH descriptor: [Craniocerebral Trauma] explode all trees
2. MeSH descriptor: [Brain Edema] explode all trees
3. MeSH descriptor: [Glasgow Coma Scale] explode all trees
4. MeSH descriptor: [Unconsciousness] explode all trees
5. MeSH descriptor: [Glasgow Outcome Scale] explode all trees
6. MeSH descriptor: [Cerebrovascular Trauma] explode all trees
7. MeSH descriptor: [Intracranial Hypertension] explode all trees
8. (head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) near/3 (injur* or trauma* or damag* or wound* or fracture* or contusion* or concuss* or pressure*)
9. (head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran* or tentori*) near/3 (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or hernia* or oedema* or edema* or swell*)
10. (glasgow near/3 (coma or outcome) near/3 (scale or score))
11. "rancho los amigos scale"
12. (diffuse near/3 axonal near/3 injur*)
13. (unconscious* or coma* or concuss* or "persistent vegetative state") near/3 (injur* or trauma* or damag* or wound* or fracture*)
14. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)
15. MeSH descriptor: [Hypothermia, Induced] explode all trees
16. MeSH descriptor: [Cryotherapy] explode all trees
17. MeSH descriptor: ⁶⁷ explode all trees
18. (hypotherm* or normotherm* or cool* or temperature* or cryother* or cryogen* or cryotreat*)
19. (refrigeration* or cryo*) near/3 anaesthes*
20. (cool* or cold*) near/3 (therap* or device* or equipment*)
21. temperature near/3 (reduc* or low*)
22. Intravenous near/3 (cold* or cool*) near/3 (fluid* or catheter*)
23. (cool* or cold*) near/3 (blanket* or neck collar* or helmet* or hood*)
24. (#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23)
25. (#14 and #24)
26. (#25)

Search Terms

The following are a list of the individual search terms used in each strategy to ensure sensitivity and specificity of each search for patient treatment and control group, as well as therapeutic management and trial design. Terms were re-evaluated for this review in May 2016 with Dr Jonathan Rhodes and Ms Shiela Fiskien.

| | | |
|------------------------|---------------------------|---------------------------------|
| allocated | damag* | neck |
| allocation | device* | normother* |
| anaesthes* | diffuse | oedema* |
| axonal | edema* | order |
| blanket* | equipment* | outcome* |
| bleed* | fluid* | 'persistent vegetative state**' |
| brain edema | forebrain* | pressure* |
| brain* | fracture* | profound induced hypothermia |
| capitis | glasgow | rancho los amigos* |
| catheter* | glasgow coma scale | random |
| cerebr* | glasgow outcome scale | randomised |
| cerebrovascular trauma | haematoma* | randomized |
| clinical | haemorrhag* | randomized controlled trial |
| clinical trial | head | randomly |
| cold* | helmet* | reduc* |
| collar* | hematoma* | refrigeration* |
| coma | hemispher* | scale* |
| coma* | hemorrhag* | score* |
| concuss* | hernia* | sequence |
| controlled | hood* | swell* |
| contusion* | hypotherm* | temperature |
| cool* | hypothermia | temperature* |
| cran* | hypothermia, induced | tentori* |
| crani* | injur* | therap* |
| craniocerebral trauma | inter-cran* | trauma* |
| cryo* | intra-cran* | trial* |
| cryogen* | intrac-cran* | unconscious* |
| cryother* | intracranial hypertension | unconsciousness |
| cryotherapy | intravenous | wound* |
| cryotreat* | low* | |

Appendix 5 Characteristics of included randomised controlled trials

The table below shows the characteristics of the included RCTs.

| Study: first author and year of publication | Method of intervention | Target or lowest body temperature achieved (°C) | Duration of TH | Maximum time between TBI and TH | Temperature management of control group (°C) | Lowest GCS score on admission (GCS score of 3–15) | Rate of rewarming |
|---|---|---|---|---------------------------------|--|---|-------------------|
| Andrews 2015 ¹ | i.v. cooling and individual centre techniques | 32–35 | 48 hours | 72 hours to 10 days | No temperature control | 3 | 0.25 °C/hour |
| Clifton 1993 ⁷³ | Cooling blankets | 32–33 | 48 hours | 6 hours | CN to 37 | 4 | 0.25 °C/hour |
| Clifton 2001 ⁷⁶ | Application of ice and gastric lavage | 33.2 ± 1.0 | 47.2 ± 3.0 hours | 6 hours | CN to 37 | 3 | 0.25 °C/hour |
| Clifton 2011 ¹²¹ | i.v. cooling, surface cooling and gastric lavage | 33 | 48 hours | 2.5 hours | CN to 37 | 3 | 0.25 °C/hour |
| Gal 2002 ⁶⁴ | Forced air cooling and circulating-water mattress cooling | 34 | 72 hours | 15 hours | CN 36.5–37.5 | 3 | – |
| Guo 2004 ¹¹⁹ | Cooling blankets | 32–34 | 24–48 hours extra following 'normal' ICP | 24 hours | No temperature control | TH: 5.3 ± 1.5 Control: 5.2 ± 1.4 | – |
| Hashigushi 2003 ¹²⁰ | Water blankets | 33.5 | 48 hours | – | CN | 3 | 1 °C/24 hours |
| Hirayama 1994 ¹¹⁵ | Cooling blankets | 32–33 | 48 hours | 6 hours | Normothermia 37–38, no further detail | GCS score of ≤ 8 | 0.25 °C/hour |
| Jiang 2000 ⁶⁹ | Cooling blankets | 33 | 3–14 days | – | CN 37–38 | 3 | – |
| Lee 2010 ¹²² | Surface cooling and ice pillows | 33 | – | – | Unclear | 4 | – |
| Liu 2006 ⁶⁰ | Cooling blankets and ice bags | 33–35 | 0–6 hours (average 4.5 hours) on 3 consecutive days | 2 hours | No temperature control | 3 | – |
| Maekawa 2015 ¹⁰⁷ | Cooling blankets | 32–34 | Ideally > 72 hours | 92 hours | CN 35.5–37 | 4 | – |
| Marion 1993 ⁷⁵ | Cooling blankets and gastric lavage | 32–33 | 24 hours | 10 hours | CN 37–38 | 3 | – |
| Marion 1997 ⁷¹ | Cooling blankets and nasogastric lavage | 32–33 | 24 hours | 6 hours | CN | 3 | 1 °C/hour |

| Study: first author and year of publication | Method of intervention | Target or lowest body temperature achieved (°C) | Duration of TH | Maximum time between TBI and TH | Temperature management of control group (°C) | Lowest GCS score on admission (GCS score of 3–15) | Rate of rewarming |
|---|--|---|---|---|--|---|-------------------|
| Qiu 2005 ⁷⁷ | Cooling blanket and/or cooling cap and/or ice bags | Brain 33–35, rectal 34.5–36 | Natural rewarming after 3–5 days (average 4.3 days) | 'Immediately' or 3–5 days (average 4.3 days) after craniotomy | Controlled to 38 | 3 | – |
| Qiu 2007 ⁵⁹ | Cooling blanket and/or cooling cap and/or ice bags | Brain 33–35, rectal 34.5–36 | 4 days | Started immediately after unilateral craniotomy | CN to 37.5 | < 6 | – |
| Shiozaki 1993 ⁷⁴ | Surface cooling | Core 34, bladder 33.5–34.5 | 48 hours | 2 hours | Unclear | – | – |
| Shiozaki 1999 ¹¹⁷ | Surface cooling | 33.5–34.5 | 48 hours | – | CN 36.5–37.5 | 4 | 1 °C/ 24 hours |
| Smrcka 2005 ¹¹⁷ | Surface cooling | 34 | 72 hours | 15 hours | Unclear | – | – |
| Zhao 2011 ¹¹⁸ | Cooling blankets | 32.5–33 | 72 hours | 6 hours | Unclear | 3 | – |
| Zhi 2003 ⁶³ | Cooling blankets | 32 | 1–7 days (average 62.4 hours ± 27.6 hours) | 20 hours | Unclear | – | 0.25 °C/ hour |
| CN, controlled normothermia; i.v., intravenous. | | | | | | | |

Appendix 6 Comparison of included trials from previous systematic reviews and meta-analyses

| Study: first author and year of publication | Study: first author and year of publication | | | |
|---|---|------------------------------|----------------------------------|----------------------------------|
| | Sydenham 2009 ¹⁵³ (Cochrane review) | Crossley 2014 ¹¹⁰ | Zhu 2016 ¹¹¹ | Watson 2018 ¹⁵⁴ |
| Adelson 2005 (HYPO1) ⁵⁶ | Y | N | N | N |
| Adelson 2005 (HYPO2) ⁵⁶ | Y | N | N | N |
| Aibiki 2000 ⁶⁸ | Y | N | N | N |
| Andrews 2015 ¹ | - | - | Y | Y |
| Biswas 2002 ⁵⁷ | Y | N | N | N |
| Clifton 1992 | Y | N | N | N |
| Clifton 1993 ⁷³ | Y | Y | Y | Y |
| Clifton 2001 ⁷⁶ | Y | Y | Y | Y |
| Clifton 2011 ¹²¹ | - | Y | N | Y |
| Gal 2002 ⁶⁴ | Y | Y | Y | Y |
| Guo 2004 ¹¹⁹ | Y | Y | N | Y |
| Harris 2009 ¹⁵⁵ | Y | N | N | N |
| Hashigushi 2003 ¹²⁰ | Y | Y | Y | Y |
| Hirayama 1994 ¹¹⁵ | Y | Y | N | Y |
| Hutchison 2008 ¹⁵⁶ | Y | N | N | N |
| Ishikura 1998 ¹⁵⁷ | Y | N | N | N |
| Jiang 2000 ⁶⁹ | Y | Y | Y | Y |
| Lee 2010 ¹²² | - | Y | Y | Y |
| Liu 2006 ⁶⁰ | N | Y | N | Y |
| Maekawa 2009 ¹⁵⁸ | N | Y | N (Maekawa 2015 ¹⁰⁷) | N (Maekawa 2015 ¹⁰⁷) |
| Maekawa 2015 ¹⁰⁷ | - | - | Y | Y |
| Marion 1993 ⁷⁵ | N | Y | N | Y |
| Marion 1997 ⁷¹ | Y | Y | Y | Y |
| Qiu 2005 ⁷⁷ | N | Y | Y | Y |
| Qiu 2006 ⁵⁸ | N | N | Y | N |
| Qiu 2007 ⁵⁹ | Y | Y | Y | Y |
| Shiozaki 1993 ⁷⁴ | Y | Y | Y | Y |
| Shiozaki 1999 ¹¹⁷ | Y | Y | Y | Y |
| Shiozaki 2001 ⁴⁹ | Y | N | Y | N |
| Smrcka 2005 ¹¹⁷ | Y | Y | Y | Y |
| Yan 2001 ⁶⁷ | Y | N | N | N |
| Zhang 2000 ⁷⁰ | Y | N | N | N |
| Zhao 2011 ¹¹⁸ | - | Y | Y | Y |
| Zhi 2003 ⁶³ | N | Y | Y | Y |
| Total studies (<i>n</i>) | 23 | 20 | 18 | 21 |
| N, no; Y, yes. | | | | |

Appendix 7 Quality assessment with academic bias

Academic bias for all 21 included RCTs is shown below. The first table outlines the quality assessment of the two new RCTs added to update the systematic review. The second table shows the characteristics of the other 19 previously included RCTs. Those scoring 14–18 were considered studies having a low risk of bias and those scoring ≤ 13 were considered having a high risk of bias.

| Quality assessment | Study: first author and year of publication | |
|--|---|-----------------------------|
| | Andrews 2015 ¹ | Maekawa 2015 ¹⁰⁷ |
| Has the control group been managed to normothermia? | Yes | Yes |
| Yes = 1; no/NS = 0 | 1 | 1 |
| Was the control group actively warmed on admission if hypothermic? | NS | NS |
| Yes = 0; NS = 1; no = 2 | 1 | 1 |
| Has the treatment arm received barbiturates in addition to TH? | No | No |
| Yes = 0; NS = 1; no = 2 | 2 | 2 |
| Are there significant differences between the treatment and control sample populations? | No | No |
| Yes = 0; no = 1; NS = 0 | 1 | 1 |
| Has the standard treatment that the control group received been clearly outlined? | Yes | Yes |
| Yes = 1; no = 0 | 1 | 1 |
| Adequacy of randomisation technique? | Adequate | Adequate |
| Adequate = 1; inadequate/unclear = 0 | 1 | 1 |
| Blinding of investigators | No | No |
| Yes = 1; no/NS = 0 | 0 | 0 |
| Blinding of participants | No | No |
| Yes = 1; no/NS = 0 | 0 | 0 |
| Blinding of outcome assessor | Yes | Yes |
| Yes = 1; no/NS = 0 | 1 | 1 |
| Blinding of data analysis | Yes | Yes |
| Yes = 1; no/NS = 0 | 1 | 1 |
| ITT analysis | Yes | Yes |
| Yes = 1; not stated but confirmed on study assessment = 1; stated but not confirmed on study assessment = 0; no/NS = 0 | 1 | 1 |
| Completion of follow-up (at 6 months if possible) | Yes, loss of 10 cases to follow-up | Yes, 100% |
| 100% = 2; > 95% = 1; < 95% = 0; no/NS = 0 | 1 | 2 |
| Reasons given when patients were excluded from enrolment, allocation follow-up or analysis? | Yes | Yes |
| Yes = 1; no = 0 | 1 | 1 |
| Has the first author published two or more RCTs that have been included in this review? | No | No |
| Yes = 0; no = 2 | 2 | 2 |
| Total score | 14 | 15 |
| Maximum score | 18 | 18 |
| NS, not stated. | | |

| Study; first author and year of publication | Has the first author published at least two RCTs that have been included in this review? | Yes = 0; no = 2 | Original score from Crossley 2014 ¹¹⁰ | Following assessment of academic bias (maximum score = 18) |
|---|--|-----------------|--|--|
| Clifton 1993 ⁷³ | Y | 0 | 8 | 8 |
| Clifton 2001 ⁷⁶ | Y | 0 | 11 | 11 |
| Clifton 2011 ¹²¹ | Y | 0 | 6 | 6 |
| Gal 2002 ⁶⁴ | N | 2 | 9 | 11 |
| Guo 2004 ¹¹⁹ | N | 2 | 10 | 12 |
| Hashigushi 2003 ¹²⁰ | N | 2 | 8 | 10 |
| Hirayama 1994 ¹¹⁵ | N | 2 | 5 | 7 |
| Jiang 2000 ⁶⁹ | N | 2 | 8 | 10 |
| Lee 2010 ¹²² | N | 2 | 8 | 10 |
| Liu 2006 ⁶⁰ | N | 2 | 6 | 8 |
| Marion 1993 ⁷⁵ | Y | 0 | 10 | 10 |
| Marion 1997 ⁷¹ | Y | 0 | 11 | 11 |
| Qiu 2005 ⁷⁷ | Y | 0 | 7 | 7 |
| Qiu 2007 ⁵⁹ | Y | 0 | 8 | 8 |
| Shiozaki 1993 ⁷⁴ | Y | 0 | 7 | 7 |
| Shiozaki 1999 ¹¹⁷ | Y | 0 | 8 | 8 |
| Smrcka 2005 ¹¹⁷ | N | 2 | 8 | 10 |
| Zhao 2011 ¹¹⁸ | N | 2 | 7 | 9 |
| Zhi 2003 ⁶³ | N | 2 | 6 | 8 |
| N, no; Y, yes. | | | | |

Appendix 8 Modified Jadad scores for included randomised controlled trials

| Study: first author and year of publication | Randomisation (2, 1 or 0 points) | Blinding (2, 1 or 0 points) | Accounting for all patients (1 point) | Total modified Jadad score (maximum 3 points) | Low quality (0, 1 or 2 points) or high quality (3 points) |
|---|----------------------------------|-----------------------------|---------------------------------------|---|---|
| Andrews 2015 ¹ | 2 | 0 | 1 | 3 | High |
| Clifton 1993 ⁷³ | 2 | 0 | 1 | 3 | High |
| Clifton 2001 ⁷⁶ | 0 | 0 | 0 | 0 | Low |
| Clifton 2011 ¹²¹ | 2 | 0 | 1 | 3 | High |
| Gal 2002 ⁶⁴ | 1 – inadequate | 0 | 0 | 1 | Low |
| Guo 2004 ¹¹⁹ | 0 | 0 | 1 | 1 | Low |
| Hashigushi 2003 ¹²⁰ | 1 – method not stated | 0 | 1 | 2 | Low |
| Hirayama 1994 ¹¹⁵ | 0 | 0 | 0 | 0 | Low |
| Jiang 2000 ⁶⁹ | 0 | 0 | 0 | 0 | Low |
| Lee 2010 ¹¹⁶ | 0 | 0 | 0 | 0 | Low |
| Liu 2006 ⁶⁰ | 2 | 0 | 0 | 2 | Low |
| Maekawa 2015 ¹⁰⁷ | 2 | 0 | 1 | 3 | High |
| Marion 1993 ⁷⁵ | 2 | 0 | 1 | 3 | High |
| Marion 1997 ⁷¹ | 2 | 0 | 1 | 3 | High |
| Qiu 2005 ⁷⁷ | 0 | 0 | 1 | 1 | Low |
| Qiu 2007 ⁵⁹ | 1 – unclear if adequate | 0 | 1 | 2 | Low |
| Shiozaki 1993 ⁷⁴ | 1 – inadequate | 0 | 1 | 2 | Low |
| Shiozaki 1999 ¹¹⁷ | 1 – inadequate | 0 | 1 | 2 | Low |
| Smrcka 2005 ¹¹⁷ | 0 | 0 | 1 | 1 | Low |
| Zhao 2011 ¹¹⁸ | 0 | 0 | 0 | 0 | Low |
| Zhi 2003 ⁶³ | 0 | 0 | 1 | 1 | Low |

A decorative graphic consisting of numerous thin, parallel green lines that curve from the left side of the page towards the right, creating a sense of movement and flow.

EME
HS&DR
HTA
PGfAR
PHR

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